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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
BETH ANNE PIPER
APPLICATION NO: 09/460,920
FILED: DECEMBER 14, 1999
FOR: METHOD FOR TREATING DIABETES

Art Unit: 1614
Examiner: R. Cook

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF PRIOR INVENTION OF BETH ANNE PIPER IN THE UNITED STATES TO OVERCOME CITED U.S. PATENT NO. 6,303,146 (37 C.F.R. § 1.131)

To the Commissioner of Patents and Trademarks:

1. This Declaration is to establish reduction to practice of the invention in this application in the United States at a date prior to July 14, 1999, that is, the effective date of U.S. Patent No. 6,303,146 (cited by the Examiner) as a reference and prior to July 15, 1998, that is the priority date claimed in U.S. Patent No. 6,303,146.

2. I, BETH ANNE PIPER, declare as follows:

3. That I am the inventor of the invention claimed in U.S. patent application Serial No. 09/460,920 filed December 14, 1999.

4. That the invention described in the Claims as filed and in Claims 37, 45 to 54, 58 to 60, 71 to 73 and 75 to 79 of application Serial No. 09/460,920 was conceived by me in the United States prior to July 15, 1998.

5. That the various teams at Bristol-Myers Squibb Company involved in the development of a low dose metformin/glyburide combination exercised due diligence in the United States prior to July 15, 1998, the priority date of U.S. Patent No. 6,303,146, and prior to July 14, 1999, the filing

date in the United States of U.S. Patent No. 6,303,146 in an actual reduction to practice of the invention on or about November 24, 1999 and exercised due diligence in a constructive reduction to practice with the filing of the subject application on December 14, 1999.

6. That prior to July 15, 1998 I informed the Project Working Group (PWG) at Bristol-Myers Squibb Company dealing with "Metformin/Glyburide Combination Tablet" that the first-line therapy protocol (CV138-019) involving the clinical testing of a metformin/glyburide combination in first-line therapy of patients having diabetes should be revised to reduce doses of glyburide to avoid hypoglycemia while still retaining required efficacy. I proposed a revised regimen based on a 12-week period of low dose combination of metformin and glyburide of 250 mg metformin and 1.25 mg glyburide for use in established diabetics (diet and exercise failures). My conception of and proposal that a low dose combination of metformin/glyburide should be employed in the first-line treatment of established diabetics is my conception of the invention as claimed in the subject application and is set out in the PWG Minutes of a meeting held prior to July 15, 1998, a copy of relevant parts of which are attached including page 2, paragraph D. entitled "Revising the 1st-Line Therapy Protocol (CV138-019)" and a copy of each of two "Overheads Used in Discussion of 1st-Line Protocol for Glyburide Combination Tablet" namely, Overhead entitled "CV138-019-Firstline Combination Therapy" and Overhead entitled "Combination Metformin-Glyburide-Clinical Utility" wherein I disclosed a low dose combination of metformin/glyburide 250 mg/1.25 mg. These relevant pages are identified as Attachments A, B and C, respectively.

7. That prior to July 15, 1998, but about one month after the PWG meeting reported in paragraph 6 above, it was reported to the PWG that tablet #4, which had a Glyburide C_{max} ratio to Hoechst's Daoril of 1.49 and a Glyburide AUC ratio to Hoechst's Daoril of 0.91, would be proposed to the FDA for clinical use under Bristol-Myers Squibb's existing IND. The above is set out in the PWG Minutes of a meeting held prior to July 15, 1998, but after the meeting reported on in paragraph 6 hereof, a copy of relevant parts of which are attached hereto and referred to as ATTACHMENT D.

It was also reported at this meeting that "the development of a lower-dose tablet (250/1.25) is being accelerated . . . ." I reported that "the clinical outline has been prepared and is ready to be sent to the FDA for comment. Attached is a copy of the clinical outline submitted to the FDA covering a low dose metformin/glyburide product for first-line therapy in Type II diabetes patients and is identified as ATTACHMENT D-1.

All of the above demonstrates due diligence in reducing the invention to practice.

8. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 7 above, a PWG meeting was held. The minutes of this meeting indicate that a letter was sent to the FDA informing the FDA that protype formulation #4 (tablet #4 in

paragraph 7) would be employed. A proposed outline for a first-line therapy study was also included in the FDA letter. The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT E sets out relevant portions of the minutes of the above PWG Meeting including the above description of the FDA letter.

9. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 8 above, another PWG meeting was held. The minutes of this meeting indicate that the FDA responded positively to the proposal to use prototype formulation #4 for clinical studies but the FDA requested that the first-line trial have an additional 12-week period (stable dose). The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT F sets out relevant portions of the minutes of the above PWG Meeting including a description of the above.

10. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 9 above, another PWG meeting was held. The minutes of this meeting indicate that the first-line trial for metformin/glyburide would be conducted as two separate trials. The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT G sets out relevant portions of the minutes of the above meeting including an outline of first-line trials.

11. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 10 above, another PWG meeting was held. The minutes of this meeting indicate that supply estimates for the first-line therapy study were finalized and that a protocol for such study was approved and would be forwarded to investigators. The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT H sets out relevant portions of the minutes of the above meeting.

12. That prior to July 15, 1998 and approximately one-two months after the PWG meeting reported on in paragraph 11 above, another PWG meeting was held. The minutes of this meeting indicate that a date for trial commencement was chosen and that an investigators' meeting was scheduled and 116 sites were recruited. The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT I sets out relevant portions of the minutes of the above meeting.

13. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 12 above, another PWG meeting was held. Internal draft notes of the meeting indicate that an investigators' meeting for the first-line clinical trial was held and that a date for start of the study was set. The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT J sets out relevant portions of the internal draft notes.

14. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 13 above, another PWG meeting was held. The minutes of this meeting

indicate that the FDA requested a change to the first-line therapy protocol and that an amendment to the protocol would be prepared. The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT K sets out relevant portions of the minutes.

15. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 14 above, another PWG meeting was held. The minutes of this meeting indicate that discussions were held with the FDA regarding the first-line study protocol (CV138-019, referred to as -019). The minutes also indicate that "the -019 study is progressing . . . and enrollment is scheduled for completion by September 30, 1998 . . . . Every effort is being made to achieve the enrollment objectives." The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT L sets out relevant portions of the minutes.

16. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 15 above, another PWG meeting was held. The minutes of this meeting indicate that there was a safety study with the metformin/glyburide combination tablet and the -019 study enrollment was progressing. The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT M sets out relevant portions of the minutes.

17. That prior to July 15, 1998 and approximately one month after the PWG meeting reported on in paragraph 16 above, another PWG meeting was held. The minutes of this meeting indicate that "study recruitment for the -019 study is 50% of expected randomized to date" and that there will be 150 sites and "abbreviated investigators' meetings are planned." The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT N sets out relevant portions of the minutes.

18. That on or about July 28, 1998, a PWG Meeting was held. The minutes of this meeting indicate that enrollment in the first-line study -019 "is progressing well and we anticipate completion by the end of September . . ." and that comparative dissolution studies with the 250/1.25 and 500 2.5 tablets will be conducted. The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT O sets out relevant portions of the minutes.

19. That on or about August 25, 1998, a PWG Meeting was held. The minutes of this meeting indicate that enrollment in the first-line study -019 "is progressing well and we anticipate completion by the end of September . . . ." The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT P sets out relevant portions of the minutes.

20. That on or about September 25, 1998, a PWG Meeting was held. The minutes of this meeting indicate that enrollment in the first-line study –019 "is progressing well and we anticipate completion ahead of schedule." Comparative dissolution studies between the 250/1.25 and 500/2.5 tablets were proposed. Stability studies were being carried out. The above demonstrates due

diligence in reducing the invention to practice. ATTACHMENT Q sets out relevant portions of the minutes.

21. That on or about October 27, 1998, a PWG Meeting was held. The minutes of this meeting indicate that "the -019 (first-line therapy) enrollment has been completed on schedule . . . . and that comparative dissolution studies between the 250/1.25 and 500/2.5 tablets is proposed. A meeting with the FDA in early November is planned to discuss these and other issues." The above demonstrates due diligence in reducing the invention to practice. ATTACHMENT R sets out relevant portions of the minutes.

22. That on or about November 24, 1998, a PWG Meeting was held. The minutes of this meeting indicate that preliminary data from the open-label (low dose 250/1.25) -019 study (first-line therapy in patients who are drug naïve and inadequately controlled with diet and exercise)

> "in which patients were directly enrolled into open-label, show that patients treated with the metformin/glyburide combination for 13 weeks have a Hemoglobin A1c value of 6.8% compared with a baseline value of 10.3%; in the same study, fasting glucose levels drop from a baseline value of 267 mg/dl to 162 mg/dl at two weeks, and 144 mg/dl at week 13. These dramatic results are expected to have a significant impact on medical opinion."

ATTACHMENT S sets out relevant portions of the minutes.

The above together with paragraphs 7 to 21 demonstrate conception of the invention and a reduction to practice prior to the effective date of the cited U.S. Patent No. 6,303,146, namely, prior to July 14, 1999.

Alternatively, the above together with paragraphs 7 to 21 demonstrate conception of the invention prior to the July 15, 1998 priority date of U.S. Patent No. 6,303,146 coupled with due diligence from prior to July 15, 1998 to a reduction to practice on or about November 24, 1998.

23. That from December, 1998 through August, 1999 the first-line study -019 continued. Evidence of continued due diligence is set out in Metformin Clinical Working Group Minutes of December 21, 1998 (ATTACHMENT S-1), January 18, 1999 (ATTACHMENT S-2), March 15, 1999 (ATTACHMENT S-3), April 20, 1999 (ATTACHMENT S-4), and May 18, 1999 (ATTACHMENT S-5), as well as in Metformin DCT (Drug Control Manufacture Team) Minutes of June 23, 1999 (ATTACHMENT S-6) and July 21, 1999 (ATTACHMENT S-7).

24. That on August 3, 1999, I sent an e-mail to Burton Rodney, patent attorney at Bristol-Myers Squibb Company (assignee of the subject application), where I indicate that I conceived of the use of a low dose metformin/glyburide combination in first-line therapy for diabetics. ATTACHMENT T is a copy of my August 3, 1999 e-mail communication to Burton Rodney.

25. That on or about August 31, 1999, a PWG Meeting was held. The minutes of this meeting indicate that

"the -019 final study report, the label, the ISE and the ISS are near completion and should be in Regulatory early next week. We are still on track for a September 30 NDA filing. Given the quality of the results described in the NDA filing and their medical importance, it is reasonable to believe that we stand a good chance of getting priority review by the FDA.

Action: Intensive effort will continue to ensure a September filing."

ATTACHMENT T-1 sets out relevant portions of the minutes.

26. That on or about September 28, 1999, a PWG Meeting was held. The minutes of this meeting indicate under the heading "Metformin Glyburide Combination Tablet" that

"the 52 volume submission and 2 CD-Rom discs are almost complete and will be shipped out on Sept. 30 for filing in Washington. The medical importance of the results described in the NDA filing should qualify this filing for Priority Review. We will know the decision of the FDA when their 45 day review is complete."

In a post-meeting note it is stated that "the NDA was filed on Sept. 30." ATTACHMENT U sets out relevant portions of the minutes.

Copies of the cover page and Introduction section of the NDA filed on September 22, 1999 covering the use of a low dose combination of metformin and glyburide in the first-line therapy of diabetes, together with pages 190 to 212 covering "Formulation Development History", are attached hereto as ATTACHMENT U-1.

As seen on page 197 of Attachment U-1, it is indicated that "prototype 4 was targeted for use in the clinical program". Prototype 4 describe a metformin/glyburide combination tablet containing 500 mg metformin and 2.5 mg glyburide where the glyburide had a particle size (μm) as follows:

"	μm
D25%	6
D50%	11
D75%	19"

On page 201 of Attachment U-1, it is indicated that "the lower strength metformin hydrochloride-glyburide 250 mg/125 mg tablet was manufactured using the same granulation employed for metformin hydrochloride-glyburide tablets 500 mg/2.5 mg, but in this case the granluation was compressed at half the press weight."

27. That from October, 1999 to December 14, 1999, Burton Rodney, patent attorney employed by Bristol-Myers Squibb Company, prepared a patent application covering a low dose metformin/glyburide combination for use in first-line therapy of diabetes and method and filed such patent application with the U.S. Patent and Trademark Office on December 14, 1999, which is a constructive reduction to practice of the invention covered by the claims of the subject application.

A copy of Mr. Rodney's Declaration to this effect accompanies this Declaration.

28. This declaration is submitted prior to Final Rejection.

The undersigned declares further that all statements made herein of her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of application Serial No. 09/460,920 or any patent issued thereon.

_____

BETH ANNE PIPER

Date:

Memorandum

Bristol-Myers Squibb Company

Pharmaceutical Research Institute

To: Distribution* **Date:**

From: G.P. Gennaro **CC:** **

Subject: Metformin Hydrochloride Reformulation (BMS 207150)
PWG Minutes Meeting

The minutes are attached.

The next regular meeting is in Princeton, Room J4.1018 at 8 am EDT
(1 pm UK; 2 pm France).

G.P. Gennaro

Attachments

***Distribution**
PWG Members
M. Altmeyer (Project Leader)
G. Gennaro (Project Manager)
M. Arnold
B. Behounek
D. Cryer
J. Figlo
N. Ford
M. Furlong
D. Greene
D. Henry
V. Jacobson
H. Kessler
P. Marathe
D. McCloskey
B. McVeety
J. Meeker
D. Mills
M. Partee
B. Piper
W. Randolph
R. Soltys
S. Spevak
P. Timmins
M. Wagner
D. Young
Lipha
T. Allavoine (Lyon)
P. Andre (Lyon)
J. Barton (New York)
T. Bataillard (Lyons)
A. Goodman (New York)
H. Howlett (Drayton)
R. Morris (Hitchin)
G. Nicholson (Hitchin)
M. Noel (Paris)
C. Pasik (Lyon)
S. White (Hitchin)
Morris Consulting
D. Bush
S. Gray

****Copy**
S. Agharkar
D. Alessi
H. Badiak
R. Barbhaiya
S. Barker
D. Barrack
D. Baylis
J. Bedard
J. Birnbaum
D. Bonk
C. Cimarusti
M. Curry
J. Daley
R. Davis
L.D. Dean (PI)
J. Donahue
J. Dubniczki
R. Feder
P. Gerencser
K. Given
J. Goldberg
J. Green
R. Gregg
E. Hagestad
M. Hartig
S. Henry
R. Hinson
J. Jackson
E. Joyce
J. Kasper
K. Kassler-Taub
G.R. Keim
K. Keisling
S. Knipple
W. Koster
F. Kuchma
R.J. Lane
P. Lapuerta
S. Lenart
J. Leslie
K.A. Leung
D. Levine
C. Linzner
R. Lipper
M. MacAskill
T. McCormick
E. McNiff
T. Mikus
R. Morrison
S. Nicholas
J. O'Sullivan
H. Pouleur
S. Rajfer
D. Reggi
P. Ringrose
B. Rodney
K. Rogosky
M. Rozencweig
P. Sibley
R. Simon
K. Weg
Y. Wen
K. White
R. Williams

H:\GPG\METFORM\-MIN97\MEM-MPWG.WPD

ATTACHMENT A

CONFIDENTIAL

BMS-207150
METFORMIN HYDROCHLORIDE REFORMULATIONS
PROJECT WORKING GROUP
MINUTES

Participating: M. Altmeyer (Leader), G. Gennaro (Manager), T. Allavoine, H. Badiak, T. Bataillard, S. Donahue, J. Dubniczki, S. Gray, D. Greene, H. Kessler, F. Kuchma, J. Leslie, P. Marathe, D. McCloskey, J. O'Sullivan, B. Piper, W. Randolph, P. Timmins, S. White, R. Williams, D. Young.

EXECUTIVE SUMMARY

Main Issues:

- Review all aspects of the glyburide combination tablet program.

Changes in Direction:

- The protocol outline for 1st-line use of the glyburide combination tablet is being modified to address the medical needs of previously untreated diabetics.

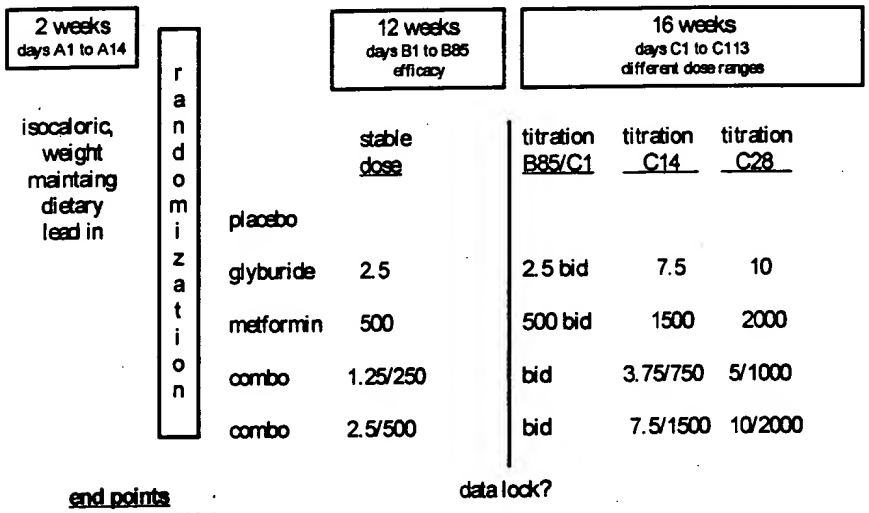
D. **Revising the 1st-Line Therapy Protocol (CV 138-019):** Dr. Piper indicated that the original outline for the 1st-line therapy protocol (cf. March and April PWG minutes) derived from the 2nd-line protocol, with the addition of a lead-in period and use of similar doses. Unfortunately, it did not address the fact that 1st-line treatment must consider the needs of a quite different and heterogeneous patient population in which treatment with higher doses of sulfonylureas could lead to hypoglycemia (i.e., some of these patients may be very drug sensitive whereas others may not). Furthermore, the dosing scheme (titration to control) was not likely to show significant differences between combination therapy and glyburide monotherapy in HA1c or primary endpoint. The dietary lead in would also be eliminated since we intend to use "established diabetics,"" who would already have experienced an adequate trial of diet and exercise.

Dr. Piper proposed a revised outline **(Attachment)** based on a 12-week period of fixed dose glyburide (2.5 mg), metformin (500 mg), low-dose combination (250/1.25 mgs), or medium-dose combination (500/2.5 mgs) in established diabetics (diet and exercise failures). With a further 16-week titration period, the study will total 30 weeks and would be 6 weeks longer than the original design.

ATTACHMENT

OVERHEADS USED IN DISCUSSION OF 1st-LINE PROTOCOL FOR GLYBURIDE COMBINATION TABLET.

CV138-019 - Firstline Combination Therapy - 7/1



end points
primary - HA1c
secondary - postprandial BS, glycosylated albumin, weight, BMI, lipid profile,
proportion of patients achieving target - FBS < 126, HA1c < 7

total time = 30 weeks

ATTACHMENT B

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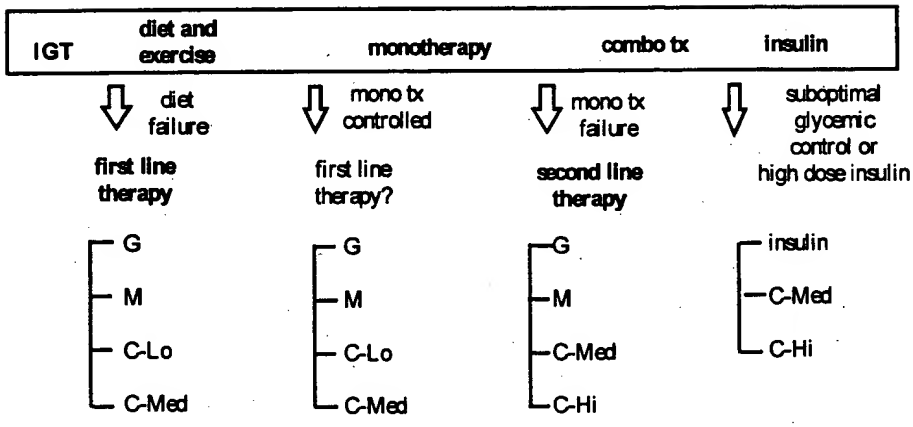
Combination Metformin-Glyburide - Clinical Utility



	combo lo	combo med	combo hi
glyburide	1.25 mg	2.5 mg	5 mg
metformin	250/300 mg	400/500 mg	500-600 mg

ATTACHMENT C

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BMS-207150
METFORMIN HYDROCHLORIDE REFORMULATIONS
PROJECT WORKING GROUP
Minutes

Participants: M. Altmeyer (Leader), G. Gennaro (Manager), T. Allavoine, M. Arnold, T. Bataillard, J. Berg, M. Brown, A. Dennis, S. Donahue, M. Furlong, D. Henry, H. Howlett, H. Kessler, F. Kuchma, J. Leslie, R. Lipper, P. Marathe, D. McCloskey, M. Partee, H. Pouleur, W. Randolph, B. Rodney, K. Rogosky, S. Spevak, M. Wagner, S. White.

EXECUTIVE SUMMARY

Main Issues:

Do any of the three newest metformin / glyburide combination tablet formulations have sufficient bioavailability of glyburide to allow us to proceed to clinical trials?

Findings:

Combination tablet #4 has a glyburide AUC of 0.85 to 0.90 that of Micronase™ when administered in the fasted or fed states. These data, supported by individual patient data showing high inherent variability of glyburide, may be sufficient to support a proposal to the FDA.

Changes in Direction:

As a consequence of the new pharmaceutical and clinical work demanded by expansion of the project to include 1st-line therapy, the projected NDA filing for the glyburide combination tablet moves from March

Decisions:

Prepare an FDA briefing document on the bioavailability of combination tablet #4 to support its use in clinical trials.

Miscellaneous:

Several metformin line extensions [oral solution, powder for constitution, chewable tablet, dispersible tablet, and soft gel capsule] are considered feasible. Marketing will select two for further development.

I. METFORMIN / GLYBURIDE COMBINATION TABLET

A. Results from Lipha-sponsored Study (Bioavailability of Combination Tablets 3 and 4 in the Fed State): S. White presented summary data from a Lipha-sponsored pharmacokinetic study to compare combination tablets 3 and 4 to glyburide (as either Upjohn's Micronase™ or Hoechst's Daonil™) and metformin (as Glucophage™). Sixteen subjects were dosed with breakfast. The AUC of combination tablet #4 was statistically bioequivalent to that of Micronase™ or Daonil™, with a mean ratio of approximately 0.9. The Cmax of combination tablet #4 was approximately 137% that of Micronase™.

Comparison	Glyburide Cmax Ratio	Glyburide AUC Ratio
Combo 3/Micronase	0.86	0.68
Combo 4/Micronase	1.37	0.89
Combo 3/ Daonil	0.93	0.69
Combo 4/ Daonil	1.49	0.91

ATTACHMENT D

Daonil/Micronase	0.92	0.97

One unanticipated result of this study was the approximate equivalence of Daonil™ to Micronase™. He also noted that the intersubject Micronase™ variability seemed lower in this study that in earlier studies. Though Lipha are awaiting a final report from Simbec, Dr. White stated that the glyburide data were final.

RECOMMENDATION: The PWG recommended that metformin/glyburide combination formulation #4 be proposed to the FDA for clinical use under our existing IND.

ACTION: A meeting has been scheduled for August 13 to further analyze the mean and individual subject data for combination tablet #4 and to prepare an FDA briefing memo on final formulation selection.

POST-MEETING NOTE: The following parameters were obtained after reanalysis of a few plasma samples for Glyburide:

Formulation	Glyburide Cmax (ng/mL) [SD]	Glyburide AUC (ng-hr/mL) [SD]
Combo 4	92.7 (30.5)	715 (252)
Metformin + Micronase™	103 (42.4)	773 (263)

Statistical comparison of Combo 4 with Micronase™ shows a point estimate (90% CI) of 0.952 (0.790, 1.147) for Cmax and 0.871 (0.750, 1.011) for AUC of Glyburide. Based on these data, the bioavailability of Glyburide from Combo 4 is deemed comparable to Micronase™ coadministered with metformin.

C. Production of Clinical Supplies (2nd-Line Therapy): Supplies of all three prototypes have been produced for the start of CV 138-011 and will be shipped to Moreton, though only one formulation will packaged. Approximately 375,000 tablets of each strength (500/5 and 500/2.5) were produced in the first run and an equivalent number will be produced in a second run. The resulting 750,000 tablets of each strength will be satisfactory to supply 1200 patients, though additional supplies will have to be prepared to support the long-term continuation segment of that study.

D. Production of Clinical Supplies (1st-Line Therapy): The development of a lower-dose tablet (250/1.25) is being accelerated and will be produced for clinical trials as a round, white tablet using available tooling. Supplies will be manufactured during the week of September 29. Tooling is being ordered for the marketed tablet, which will be colored and capsule-shaped (13 x 6.5 mm).

I. Clinical Study CV138-019 (1st Line): The clinical outline has been prepared and is ready to be sent to the FDA for comment. However, FDA acceptance of our final dosage form must come first, though W. Randolph will have the briefing document for the 1st-line protocol ready to submit as soon as the FDA is receptive.

J. Revised Projection for NDA Filing: As a immediate consequence of the addition of a 1st-line study and new, lower-dose tablet, the projection for the NDA filing must be changed from M to June,

This is dictated, in equal measure, by the need to develop, prepare, and package clinical supplies (including the new 250/1.25 mg tablet) and by the need to set up the 1st-line study, from securing FDA input through setting up the study sites.

FIXED DOSE METFORMIN/GLYBURIDE COMBINATION PRODUCT FOR FIRST LINE THERAPY IN NIDDM PATIENTS WHO HAVE FAILED DIET AND EXERCISE PROTOCOL SYNOPSIS (CV138-019)

Title: Safety and Efficacy of Fixed Metformin/Glyburide Combination Products as First Line Therapy in NIDDM Patients Who Have Failed Glycemic Control on Diet and Exercise

Hypothesis: Administration of a low dose combination product of metformin with glyburide will improve glycemic control in patients with NIDDM who have failed control with diet and exercise.

Rationale: Previous studies have demonstrated improved glycemic control when metformin is used in combination with sulfonylurea in patients who have failed sulfonylurea therapy alone. Treatment with a low dose combination product may be expected to achieve glycemic control as first line therapy with lower doses of each drug than when used in monotherapy because the mechanisms of drug action are complementary.

Objectives:

1) To compare glycemic control between metformin, glyburide, and two dosage strengths of the combination of metformin plus glyburide (250/1.25 mg and 500/2.5 mg) in a patient population of NIDDM who have failed glycemic control with diet and exercise.

2) To assess the safety and tolerability of treatment of NIDDM with a metformin/glyburide combination product.

Study Design:

- Five-arm, double-blind parallel group design in patients with NIDDM. Study will be multi centered and will be conducted in the USA.
- Dietary lead-in phase (Period A) to consist of a 2-week, isocaloric, weight maintaining diabetes prudent diet.
- Double-blind stable dose phase (Period B), of 4 weeks duration, with randomization (1:1:1:1:1) to placebo, glyburide 2.5 mg, metformin 500 mg and combination metformin glyburide therapy in 2 dosage strengths (250/1.25 mg and 500/2.5 mg). During Period B patients will be maintained on a stable dose of medication; this is to allow comparison of the combination product to its individual components at a stable dose. Fructosamine will be the outcome measure of glycemia.
- Double-blind titration phase (Period C), 16 weeks duration. During

Period C patients will be titrated, if indicated, to the next dosage strength of the medication they are on to achieve glycemic control. The potential maximal doses achieved will be glyburide 10 mg, metformin 2000 mg, and combinations 5/1000 mg and 10/2000 mg.

Inclusion Criteria:

- Males, females 30-70 years
- Established NIDDM of at least 3 months duration but no longer than 10 years.
- FPG between 140-280 mg/dl and HbA_{1C} between 7.0-11%
- C-peptide > .80 ng/ml at screening
- Failure to achieve adequate glycemic control with an adequate trial of diet and exercise.
- Normal renal function (S_{CR} < 1.5 mg/dl males, S_{CR} < 1.4 mg/dl females)
- AST and ALT less than 2 x upper limit of normal
- Body Mass Index < 35 kg/m^2

Exclusion Criteria:

- Symptomatic NIDDM defined as marked polyuria, polydipsia and greater than 10% weight loss
- Diagnosis of NIDDM within the past 3 months or greater than 10 years ago.
- Significant liver disease
- Significant cardiovascular disease
- Malignant diseases
- Alcohol and/or substance abuse
- History of diabetic ketoacidosis or hyperosmolar, nonketotic coma
- Sensitivity to biguanides and/or sulfonylurea
- Current therapy with antihyperglycemic agents or administration of antihyperglycemic agents in the last 2 months

Study Medication Dose Forms:

- Placebo
- Metformin 500 mg
- Glyburide 2.5 mg
- Combination metformin/glyburide 250/1.25 mg
- Combination metformin/glyburide 500/2.5mg

Study Conduct: Eligibility will be determined at screening. Potential candidates will be interviewed by a dietician and instructed to follow an isocaloric weight maintaining diabetes prudent diet for 2 weeks (Period A). If FPG levels on screening and visit A15 are between 140-280 mg/dl, HbA_{1c} is between 7.0-11%, c-peptide >.80 ng/ml and no exclusion criteria are present at enrollment, then subjects will be eligible to enter the 4 week double-blind stable dose treatment phase (Period B). Subjects will be randomly assigned to either placebo, glyburide 2.5 mg, metformin 500 mg, metformin 500 mg/glyburide 2.5 mg combination or metformin 250 mg/glyburide 1.25 mg combination. This dose will be taken with their morning meal. After 4 weeks of therapy patients will enter a 16 week dose titration phase, Period C, to achieve glycemic control. Titration will be performed every two weeks for the first 4 weeks of double-blind therapy (Visits B85/C1, C14, and C28). If it is necessary to titrate dose up then the second tablet will be given with the evening meal. The third tablet will be added to the morning meal and the fourth dose with the evening meal. The criterion for titration to next dose level is FPG > 140 mg/dl. Doses will be maintained for a FPG < 140; there will be no titration downward unless there is documented hypoglycemia. The maximum titrated daily doses will be glyburide 10 mg, metformin 2000 mg, metformin 1000 mg/ glyburide 5 mg, and metformin 2000 mg/glyburide 10 mg. Approximately 730 subjects (146 per arm to allow 138 evaluable subjects per treatment arm) will be randomized to double-blind therapy at ± 70 study sites.

Outcomes: In Period B, assessment of the contributions of each component in the combination product will be made by comparing the mean change in fructosamine or glycosylated albumin in patients receiving the metformin 500mg/glyburide 2.5 mg to the changes in the metformin and glyburide monotherapy groups. The lower dose combination product (metformin 250 mg /glyburide 1.25 mg) will be compared to placebo to see if patients can benefit from these low doses. In period C, after dose titration to optimize FPG, mean changes in HbA_{1c} will be assessed between dosing arms to assess efficacy of long term glycemic control. Secondary outcomes to include FPG, post-prandial plasma glucose, lipid profile (Chol, TG, LDL-CHOL, HDL-CHOL), body weight, and the proportion of patients achieving the target profile of FPG <126 and HbA_{1c} <7.

SAFETY AND EFFICACY OF METFORMIN/GLYBURIDE COMBINATION PRODUCTS AS FIRST LINE THERAPY IN NIDDM PATIENTS WHO HAVE FAILED GLYCEMIC CONTROL WITH DIET AND EXERCISE

CV138-019	A - Diet 2 weeks		B - Stable Dose 4 weeks					C - Dose Titration 16 weeks					
Event	screen/ enroll	A14	B1	B8	B15	B22	B29	C1	C15	C29	C57	C85	C 113
Consent	X												
Dietary consult	X												
Full Hx & PE	X												X
Brief Hx and PE							X				X		
C-peptide	X												
FPG	X	X		X	X	X	X		X	X	X	X	X
HbA1c	X	X					X				X		X
Fructosamine		X		X	X	X	X		X	X	X		X
Glycosylated albumin		X		X	X	X	X		X	X	X		X
PPPG		X					X						X
Lipids		X					X				X		X
Weight	X	X					X						X
Standard Safety Labs	X	X					X						X
Adverse Events		X				X	X	X	X	X	X	X	X
12 lead ECG	X												X
Chest X-ray	X												
Pregnancy Test		X					X		X		X		X
Randomize			X										
Medication Dispensing			X			X	X	X	X	X	X	X	
Medication Count						X	X	X	X	X	X	X	X

Memorandum

Bristol-Myers Squibb Company

Pharmaceutical Research Institute

To: Distribution* **Date:**

From: G.P. Gennaro **CC:** **

Subject: Metformin Hydrochloride Reformulation (BMS 207150)
PWG Minutes Meeting

COPY

The minutes are attached.

The next regular meeting is in Princeton, Room J4.1018 at 8:30 am EDT
(1:30 pm UK; 2:30 pm France).

G.P. Gennaro

Attachments

*Distribution
PWG Members
M. Altmeyer (Project Leader)
G. Gennaro (Project Manager)
M. Arnold
B. Behounek
D. Cryer
J. Figlo
N. Ford
M. Furlong
D. Greene
D. Henry
V. Jacobson
H. Kessler
P. Marathe
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B. McVeety
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J. Daley
R. Davis
L.D. Dean (PI)
J. Donahue
J. Dubniczki
R. Feder
P. Gerencser
K. Given
J. Goldberg
J. Green
R. Gregg
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J. Kasper
K. Kassler-Taub
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J. Leslie
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C. Linzner
R. Lipper
M. MacAskill
T. McCormick
E. McNiff
T. Mikus
R. Morrison
S. Nicholas
H. Pouleur
S. Rajfer
D. Reggi
P. Ringrose
B. Rodney
K. Rogosky
M. Rozencweig
P. Sibley
R. Simon
K. Weg
Y. Wen
K. White
R. Williams

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ATTACHMENT E

CONFIDENTIAL

BMS-207150 (METFORMIN HYDROCHLORIDE REFORMULATIONS) PROJECT WORKING GROUP MINUTES

Participating: M. Altmeyer (Leader), G. Gennaro (Manager), S. Agharkar, T. Allavoine, M. Arnold, M. Brown, S. Donahue, M. Furlong, S. Gray, D. Greene, D. Henry, F. Kuchma, J. Leslie, G. Nicholson, P. Marathe, C. Pasik, B. Piper, W. Randolph, K. Rogosky, S. Spevak, P. Timmins, M. Wagner, Y. Wen, S. White, R. Williams, D. Young.

EXECUTIVE SUMMARY

Findings:

- FDA have been provided with formulation and protocol information for the metformin/glyburide program.

I. METFORMIN / GLYBURIDE COMBINATION TABLET

A. **Notification to FDA:** Prototype formulation #4 was adopted as the preferred formulation for the metformin/glyburide combination tablet. A summary report from the BMS bioavailability study in the fasted state was sent to the FDA on September 2 along with a draft report from Simbec on the bioavailability of that same formulation in the fed state. The FDA letter also included amendments to the 2nd-line protocol that have now been approved within BMS to allow prior treatment with metformin and to modify the downward titration schedule. Finally, the FDA letter included our proposed outline for a 1st-line therapy study.

This information has been provided to the FDA to give them an opportunity to comment on the suitability of the adopted formulation and to provide feedback on the proposed clinical program to support registration for 2nd-line and 1st-line use.

ATTACHMENT E

Memorandum

Bristol-Myers Squibb Company

Pharmaceutical Research Institute

To: Distribution* **Date:**

From: G.P. Gennaro **CC:** **

Subject: Metformin Hydrochloride Reformulation (BMS 207150)
PWG Minutes Meeting

The minutes are attached.

The next regular meeting is in Princeton, Room J4.1018 at 8:30 am EDT
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G.P. Gennaro

Attachments

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P.S. Ringrose
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M.B. Stewart

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D.J. Hayden
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R.E. Hinson
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Q.C. Oswald
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M.S. Potter
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L.D. Dean
C. Linzner
T. Mikus
D. Reggi

ATTACHMENT F

CONFIDENTIAL

BMS-207150 (METFORMIN HYDROCHLORIDE REFORMULATIONS) PROJECT WORKING GROUP MINUTES

Participating: M. Altmeyer (Leader), G. Gennaro (Manager), T. Allavoine, T. Bataillard, M. Brown, J. Daley, S. Donahue, S. Gray, D. Greene, D. Henry, H. Howlett, C. Hubert. T. Hulot, H. Lee, P. Marathe, G. Nicholson, M. Noel, C. Pasik, B. Piper, W. Randolph, M. Ritzert, S. Spevak, M. Staten, P. Timmins, M. Wagner, N. Wiernsperger, Y. Wen, R. Williams.

EXECUTIVE SUMMARY

Main Issues:

- Readdress the development timelines for the metformin/glyburide combination tablet and the metformin novel oral dosage form.

Findings:

- The FDA-mandated extension of the treatment period for the metformin/glyburide tablet in the 1st-line study will place the projected NDA filing towards the end c

I. METFORMIN/GLYBURIDE COMBINATION TABLET

M. Altmeyer opened the meeting by congratulating team members on developing the metformin/glyburide combination tablet that the FDA has now cleared for further clinical development (see below).

A. **FDA Response to BMS Proposals:** On September 25th, the FDA responded positively to our proposal to use prototype formulation 4 for clinical studies. They were satisfied with the study design for the 2nd-line trial, but requested that the 1st-line trial, which was to have terminated with a dose titration period to the primary end point (Period C), have an additional 12 week, stable dose period (Period D) **[See Attachment 1]**. This FDA-mandated addition will extend the overall duration of the study, though an interim analysis after Period C should help in minimizing the report preparation time after data lock.

Proprietary Information - Not for further distribution.

C. **Preparation For 1st-line Study [CV138-019]:** The duration of phases in the 1st-line trial now stands at:

Dietary Lead-in (Period A) - 2 Weeks
Stable Dose (Period B) - 4 Weeks
Dose Titration (Period C) - 16 Weeks
Stable Dose (Period D) - 12 Weeks

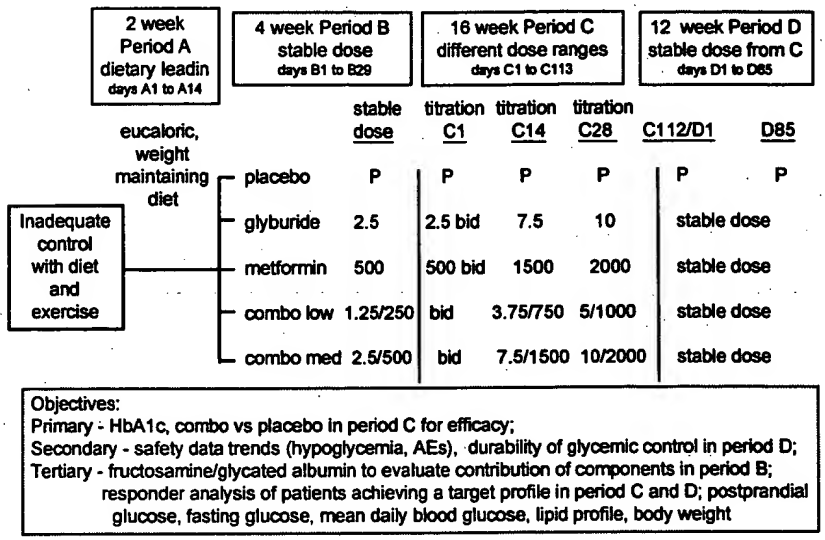
An interim analysis on the primary end-point will be conducted after the last patient completes Period C. Consideration was given to conducting Period D as an open label phase, but the staggered enrollment and treatment schedule and the complexity of packaging ultimately led B. Piper to recommend that patients continue to receive blinded supplies until the end of Period D.

M. Wagner and B. Piper have estimated the large clinical supplies requirements now dictated by the new study design, including long-term extensions for both 1st-line and 2nd-line trials.

ATTACHMENT 1: Outline of 1st-Line Study for Metformin/Glyburide

CV138-019 10/7/97

Fixed Combination Metformin/Glyburide for Firstline Therapy



Objectives:
Primary - HbA1c, combo vs placebo in period C for efficacy;
Secondary - safety data trends (hypoglycemia, AEs), durability of glycemic control in period D;
Tertiary - fructosamine/glycated albumin to evaluate contribution of components in period B; responder analysis of patients achieving a target profile in period C and D; postprandial glucose, fasting glucose, mean daily blood glucose, lipid profile, body weight

Proprietary Information - Not for further distribution.

Memorandum

Bristol-Myers Squibb Company

Pharmaceutical Research Institute

To: Distribution* **Date:**

From: G. Gennaro/S. Spevak **CC:** DOC & Copy**

Subject: Metformin Hydrochloride Reformulation (BMS 207150)
PWG Minutes Meeting

The minutes are attached.

The next regular meeting is in Princeton, Room J4.1018 at 8:30 am EST
(1:30 pm UK: 2:30 pm France).

*DISTRIBUTION

PWG Members
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L.D. Dean
C. Linzner
T. Mikus
D. Reggi
M. Rosencweig

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ATTACHMENT 6

CONFIDENTIAL

BMS-207150 (METFORMIN HYDROCHLORIDE REFORMULATIONS) PROJECT WORKING GROUP MINUTES

Participating: M. Altmeyer (Leader), G. Gennaro (Manager), S. Agharkar, T. Allavoine, M. Arnold, T. Bataillard, M. Brown, J. Daley, A. Dennis, S. Donahue, S. Gray, D. Greene, D. Henry, H. Howlett, T. Hulot, P. Marathe, G. Nicholson, C. Pasik, B. Piper, W. Randolph, S. Raff, M. Ritzert, K. Rogosky, S. Spevak, S. Srivastava, M. Staten, P. Timmins, M. Wagner, Y. Wen, R. Williams, W. Winter.

EXECUTIVE SUMMARY

Main Issues:

- Make a 'Go/No Go' recommendation on further development of a novel oral dosage form for once daily administration. Monitor progress in initiating the metformin/glyburide program.

Changes in Direction:

- To reduce the length and complexity of the 1st-line trial for metformin/glyburide, the study will now be conducted as two separate trials.

Proprietary Information - Not for further distribution.

II. METFORMIN / GLYBURIDE COMBINATION TABLET

A. **Status of 2nd Line Trial (CV138-011):** B. Piper reported that enrollment (glyburide lead-in period) has now commenced at some sites.

B. **Proposals for 1st Line Trials (CV138-019; CV138-025):** The design of the 1st-line trial, which had recently become quite lengthy and complicated to address FDA requests for increased patient exposure, has now been simplified by dividing it into two separate trials. **[Attachment 3]** CV138-019 will incorporate a 24-week treatment period with an interim analysis at 16 weeks and a switch of patients from placebo to active treatment as indicated. CV138-025 will maintain a fixed dose for the full 14 weeks of treatment, but will maintain patients at either 250/1.25 mgs b.i.d or 500/2.5 mgs b.i.d. during a long-term extension period.

ATTACHMENT 3: Metformin / Glyburide - Outline of 1st Line Trials

Proprietary Information - Not for further distribution.

CV138-019 - Safety and Efficacy of a Fixed Combination Metformin/Glyburide Product for Firstline Therapy (n=300-1000)

2 week Period A dietary leadin days A1 to A14

24 week Period B
Double-blind treatment period - Efficacy, safety, tolerability, durability
days B1 to B169

Inadequate control with diet/ exercise (HbA1c 7-11%)

	B1	titration B15	titration B22	titration B29	B57	B85	B113	B141	B169
placebo	P	P bid	P	P		stable dose		stable dose	
glyburide	2.5	2.5 bid	7.5	10		stable dose		stable dose	
metformin	500	500 bid	1500	2000		stable dose		stable dose	
combo low	1.25/250	bid	3.75/750	5/1000		stable dose		stable dose	
combo med	2.5/500	bid	7.5/1500	10/2000		stable dose		stable dose	

Objectives:
Primary - HbA1c, combo vs placebo at week16 (B112) for efficacy;
Secondary - safety data trends (hypoglycemia, AEs),
withdrawl due to lack of efficacy,
durability of glycemic control B112 to B168;
Tertiary - glycemic control - comparisons of fructosamine,
PPPG and insulin, FBG, mean daily blood glucose ;
responder analysis of patients achieving a target profile;
lipid profile, body weight

interim analysis at 16 weeks for primary endpoint and evaluation for lack of efficacy; switch to active combo if indicated

Patients withdrawn for lack of efficacy or completing the 24 week treatment phase are eligible for a one year open label combination therapy long term extension phase

Memorandum

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

To: Distribution*

Date:

From: G. Gennaro/S. Spevak

CC:

Subject: Metformin Hydrochloride Reformulation (BMS 207150)
PWG Minutes Meeting

The minutes are attached.

The next regular meeting is in Princeton, Room J4.1018 at 8:30 am EST
(1:30 pm UK: 2:30 pm France).

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ATTACHMENT H

CONFIDENTIAL

BMS-207150 (METFORMIN HYDROCHLORIDE REFORMULATIONS) PROJECT WORKING GROUP MINUTES

Participants: M. Altmeyer (Leader), G. Gennaro (Manager), S. Agharkar, T. Allavoine, T. Bataillard, M. Brown, N. Cottely, R. Davis, S. Donahue, M. Furlong, S. Gray, D. Henry, H. Lee, P. Marathe, G. Nicholson, B. Piper, P. Prabharkaran, W. Randolph, S. Raff, K. Renz, M. Ritzert, S. Spevak, S. Smith, S. Srivastava, M. Staten, P. Timmins, M. Wagner, S. White.

EXECUTIVE SUMMARY

Main Issues:

II. METFORMIN / GLYBURIDE COMBINATION TABLET

Supplies estimates have now been finalized for the single, large 1st-line therapy study. The protocol for that study has been approved by the PRC and will be forwarded to investigators in December while we simultaneously continue to recruit additional sites.

M. Wagner indicated that he and S. White have refined the trans-Atlantic shipping arrangements for bulk drug product and that a steady stream of clinical supplies is now assured.

Proprietary Information - Not for further distribution.

Memorandum

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

To: Distribution*
From: G. Gennaro/S. Spevak

Date:
CC:

Subject: Metformin Hydrochloride Reformulation (BMS 207150)
PWG Minutes Meeting

The minutes are attached.

The next regular meeting is in Princeton, Room J4.1618 at 8:30 am EST
(1:30 pm UK: 2:30 pm France).

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R.J. Lane
J.M. Lasker
Q.C. Oswald
P.S. Ringrose
D.P. Tunnell
P.O. Wallstrom
K.E. Weg
R.E. Winningham

**DOC
L.G. Arnold
R.H. Barbhaiya
J.F. Bedard
J. Birnbaum
T.D. Bjornsson
G.G. Burnham
J. Caldarella
R.M. Canetta
C. Cimarusti
M.E. Curry
J.J. Donahue
G.C. Dunbar
R.M. Echols
W. Epinette
K.M. Given
J.D. Goldberg
E. Hagestad
M. Hartig
J.D. Jackson
G.R. Keim
K. Kassler-Taub
W.H. Koster
R.A. Lipper
K.A. Leung
E.F. McNiff
J. Petrin
G. Picot
H. Pouleur
S.I. Rajfer
P.S. Ringrose
A.C. Santopolo
A. Schwebig
R.L. Simon
L.F. Smaldone
M.B. Stewart
S. Wanless

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D.J. Barrack
A.G. Bodnar
L.D. Dean
C. Linzner
T. Mikus
D. Reggi
M. Rosenweig

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ATTACHMENT I

CONFIDENTIAL

BMS-207150 (METFORMIN HYDROCHLORIDE REFORMULATIONS) PROJECT WORKING GROUP MINUTES -

Participants: M. Altmeyer (Leader), G. Gennaro (Manager), T. Allavoine, M. Brown, D. Cryer, I. Delaet, A. Dennis, S. Donahue, M. Furlong, S. Gray, D. Henry, H. Howlett, P. Marathe, G. Nicholson, C. Pasik, B. Piper, P. Prabharkaran, W. Randolph, S. Raff, K. Renz, S. Spevak, S. Srivastava, M. Staten, R. Williams.

EXECUTIVE SUMMARY

Main Issues:

- Increase enrollment in the metformin/glyburide clinical trial.

II. METFORMIN / GLYBURIDE COMBINATION TABLET

Dr. Misbin at the FDA is reviewing these proposed changes.

Clinical R&D have created advertising budgets to promote enrollment. Additional sites will be added and inactive sites will be dropped.

B. First-Line Clinical Trial (CV138-019): This trial should commence on 2/23, provided clinical supplies for Period C are received soon from Lipha.

An Investigators' Meeting will be held on 2/14 and 2/15 in Arlington, VA. One hundred sixteen sites have been recruited.

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INTERNAL DRAFT NOTES

The following are internal draft notes for use within the Metformin Project Working Group. Beginning this month, distributed PWG minutes will be replaced by a PWG Meeting Summary. The PWG Meeting Summary will concentrate on issues and actions and will exclude status updates.

CONFIDENTIAL

BMS-207150
METFORMIN HYDROCHLORIDE REFORMULATIONS
PROJECT WORKING GROUP
DRAFT NOTES

Participating: M. Altmeyer (Leader), G. Gennaro (Manager), T. Allavoine, T. Battailard, I. Delaet, S. Donahue, D. Greene, D. Henry, H. Howlett, P. Marathe, C. Pasik, B. Piper, P. Prabharkaran, W. Randolph, S. Raff, K. Renz, M. Ritzert, S. Spevak, S. Srivastava, M. Staten, P. Timmins, M. Wagner, R. Williams.

II. METFORMIN / GLYBURIDE COMBINATION TABLET

B. First-Line Clinical Trial (CV138-019): The investigators' meeting, at which 115 potential sites were represented, went quite well. The study is projected to start during the first week in March. A Video News Release (VNR) will be prepared to promote enrollment.

C. Manufacturing Sites: A stability trial will be conducted in Humacao during April to qualify this site for commercial manufacture of the combination tablet.

ATTACHMENT J

Memorandum

Bristol-Myers Squibb Company
Pharmaceutical Research Institute

To: Distribution* **Date:**

From: G. Gennaro **CC:**

Subject: Metformin Hydrochloride Reformulations (BMS 207150)
PWG Meeting Summary

The meeting summary is attached.

The next regular meeting is in Princeton, Room J4.1018 at 8:30 am EDT
(1:30 pm UK: 2:30 pm France).

***DISTRIBUTION**

PWG Members
M. Altmeyer (Project Leader)
G. Gennaro (Project Manager)
S. Agharkar
M. Brown
N. Cottely
J. Daley
S. Donahue
D. Henry
P. Marathe
B. Piper
S. Raff
W. Randolph
K. Renz
S. Srivastava
M. Staten
P. Timmins
M. Wagner
R. Williams

Lipha
T. Allavoine (Lyon)
J. Barton (New York)
T. Bataillard (Lyons)
A.C. Benichou
A. Goodman (New York)
H. Howlett (Drayton)
T. Hulot (Lyon)
G. Nicholson (Hitchin)
C. Pasik (Lyon)
S. White (Hitchin)

Morris Consulting
D. Bush
S. Gray

WWMOC
H.M. Abdou
S.L. Barker
S. Bear
L.T. DiFazio
P.R. Dolan
R. Feder
D.J. Hayden
R.E. Hinson
R.J. Lane
J.M. Lasker
Q.C. Oswald
P.S. Ringrose
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J.D. Goldberg
E. Hagestad
M. Hartig
J.D. Jackson
K. Kassler-Taub
G.R. Keim
W.H. Koster
R.A. Lipper
K.A. Leung
E.F. McNiff
J. Petrin
G. Picot
H. Pouleur
S.I. Rajfer
P.S. Ringrose
A.C. Santopolo
A. Schwebig
R.L. Simon
L.F. Smaldone
M.B. Stewart
S. Wanless

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M. Arnold
D.J. Barrack
A.G. Bodnar
L.D. Dean
J. Figlo
M. Furlong
R. Gimbel
D. Greene
D. Kelly
C. Linzner
J. Meeker
T. Mikus
D. Mills
M. Partee
D. Reggi
B. Rodney
K. Rogosky
M. Rosencweig
R. Soltys
J. Spagnoulo
J. Timko
D. Young

ATTACHMENT K

METFORMIN HYDROCHLORIDE REFORMULATIONS
Project Working Group Meeting Summary

MILESTONES

GOALS

itiate 1st-line Trial for Metformin/Glyburide Tablet (-019)

Initiate Phase III Clinical Trials for Biphasic Tablet

METFORMIN/GLYBURIDE PHASE III TRIALS

Issue: The FDA has requested a change to the -019 (1st-line therapy) protocol that would specify discontinuation criteria for patients being inadequately controlled. It was not certain whether they would insist on a single criterion (*e.g.*, maximum fasting blood glucose level or a drop in fasting blood glucose) or might accept some combination of the two. This issue may become important as it might ultimately impact the number of patients completing the study on placebo or on the least effective monotherapy regimens.

Action: B. Piper will immediately develop and propose a protocol amendment to satisfy FDA's requested changes to the discontinuation criteria.

PROPRIETARY INFORMATION - NOT FOR FURTHER DISTRIBUTION

Project Leader: Mark Altmeyer

Project Manager: Joe O'Sullivan

METFORMIN HYDROCHLORIDE REFORMULATIONS
PWG Meeting Summary

MILESTONES
The metformin/glyburide first line study began on

METFORMIN/GLYBURIDE

Issue: What is the status of the discussions with the FDA regarding withdrawal criteria in the proposed studies and how is enrollment progressing? Can additional information of value be extracted from these studies?

Action: Discussions have been held with the FDA regarding the protocols for studies -011 and -019 and modifications and criteria for discontinuation have been agreed upon.

In the -019 study, screening will be carried out on a population with FBG less than or equal to 240 mg/dl; after four weeks and FBG still greater than 200mg/dl patients (and without a drop of 20 mg/dl) can/must be removed from the study and they enter an open label treatment phase.

Enrollment in -011 is about a month behind schedule but we expect to reach the 400 projected subject number during the nine month planned.

PROPRIETARY INFORMATION - NOT FOR FURTHER DISTRIBUTION

ATTACHMENT 2

The -019 study enrollment is progressing (43 screened, 15 enrolled and two randomized) and enrollment is scheduled for completion by September 30, 1998 when at least 500 patients (and not more than 750) will have been randomized. A new CRO will be involved in the recruitment effort. Every effort is being made to achieve the enrollment objectives.

Although Outcomes Research was not involved in the protocol writing stage, it will be useful to convene with them and Dr. Marsha Testi, a well known scholar in the Outcomes field, to explore opportunities emerging from the ongoing studies.

Project Leader: Mark Altmeyer

Project Manager: Joe O'Sullivan

METFORMIN HYDROCHLORIDE REFORMULATIONS
PWG Meeting Summary

METFORMIN/GLYBURIDE

Issue: There are two safety studies with the combination tablet, a second-line clinical trial CV138 -011 and a first-line trial, CV138-019, and close attention is being paid to enrollment rates.

Action: Enrollment in -011 is about 76% complete; an additional 22 sites will be added but only four or five of these will receive drug the first week in June, bringing the total to 83 active sites. We expect to reach the 400 projected subject number on time.

The -019 study enrollment is progressing (157 subjects have been screened and forty randomized) and enrollment is scheduled for completion by September 30, 1998 when at least 500 patients (and not more than 750) will have been randomized. Of the 116 planned sites, 56 are active and information packages will be sent to an additional 50 sites within the week. There are significant challenges in meeting our enrollment objectives and additional recruitment efforts are being made with radio and television advertisements. Discussions will be held with Marketing personnel to come up with new ways to help enrollment.

PROPRIETARY INFORMATION - NOT FOR FURTHER DISTRIBUTION

ATTACHMENT M

Project Leader: M. Altmeyer

Project Manager: J. O'Sullivan

Metformin Hydrochloride Reformulation (BMS-207150)

PWG Meeting Summary

METFORMIN/GLYBURIDE

Issue: There are two safety and efficacy studies with the metformin/glyburide combination tablet, a first-line trial, -019 and a second-line trial, -011. A successful enrollment is required to stay within the timelines.

Action: Enrollment in the –011 will be completed on July 24. We now have 511 enrolled and 413 have been randomized.

Study recruitment for the –019 study is 50% of expected randomized to date. There are 100 sites currently active and we are adding new sites for a total of 150 sites. Abbreviated investigator's meetings are planned, one for East Coast sites on July 24 and a second for West Coast sites yet to be scheduled.

ATTACHMENT N

Project Leader: M. Altmeyer

Project Manager: J. O'Sullivan

Metformin Hydrochloride Reformulation (BMS-207150)

PWG Meeting Summary

July 28, 1998

DECISIONS

Drug combination strengths of 250/1.25, 500/2.5, 500/5 and 500/7.5 have been selected for metformin/glyburide;

METFORMIN/GLYBURIDE

Issue: There are two safety and efficacy studies with the metformin/glyburide combination tablet, a first-line trial, -019 and a second-line trial, -011. Due to start in August 1998 is the Micronase bioavailability study, CV137-037. Stability studies with various batches of drug are ongoing. What is the patent status of the combination?

Action: Enrollment in the –011 has been completed; we now have greater than 500 randomized subjects at 80 sites. The -019 enrollment is progressing well and we anticipate completion by the end of September; there are 95 active sites, 556 screened, 240 enrolled and 175 randomized. Drug supply to the sites is progressing satisfactorily.

ATTACHMENT O

Project Leader: M. Altmeyer

Project Manager: J. O'Sullivan

Metformin Hydrochloride Reformulation (BMS-207150)

PWG Meeting Summary

August 25, 1998

METFORMIN/GLYBURIDE

Issue: There are two safety and efficacy studies with the metformin/glyburide combination tablet, a first-line trial, -019 and a second-line trial, -011. Details of the CMC package for NDA filing need to be reviewed with the FDA before submission.

Action: Enrollment and randomization in the –011 study has been completed; we now have 634 subjects at 80 sites; 180 of these have completed treatment and the LPLV will be December 1. The -019 enrollment is progressing well and we anticipate completion by the end of September; there are 155 active sites, 928 screened, 371 enrolled and 290 randomized. Drug supply to the sites is progressing satisfactorily.

A discussion was held recently with representation from CMC Regulatory, Pharmaceutics R&D (Moreton) and MAP to develop plans for a meeting with the FDA. We would like to review our plans for the CMC sections of the NDA submission with them. We propose to do bioavailability studies with

ATTACHMENT P

Project Leader: M. Altmeyer

Project Manager: J. O'Sullivan

Metformin Hydrochloride Reformulation (BMS-207150)

PWG Meeting Summary
September 25, 1998

The first line trial with the combo is ahead of schedule.

METFORMIN/GLYBURIDE

Issue: Enrollment and randomization in the –011 (second-line) study has been completed; we now have 634 subjects at 80 sites; 223 of these have completed treatment and the LPLV will be December 1. The -019 (first-line trial) enrollment is progressing well and we anticipate completion ahead of schedule; there are 155 active sites, 1500 screened, 653 enrolled and 502 randomized; 125 are in open-label. Drug supply to the sites is progressing satisfactorily.
CMC Regulatory, Pharmaceutics R&D (Moreton) and MAP have developed plans for a pre-NDA-meeting with the FDA. We propose to do bioavailability studies with the 500/2.5 and the 500/5 tablets and comparative dissolution studies between the 250/1.25 and 500/2.5 tablets. A meeting with the FDA in late October/early November is planned to discuss these and other issues. Stability studies at room temperature or under stress continue and the data generated looks good.

Action: Meet with the FDA to discuss study plans leading to NDA filing (M. Brown).

ATTACHMENT Q

Project Leader: M. Altmeyer

Project Manager: J. O'Sullivan

Metformin Hydrochloride Reformulation (BMS-207150)

PWG Meeting Summary

October 27, 1998

METFORMIN/GLYBURIDE

Issue: Enrollment and randomization in the –011 (second-line therapy) study has been completed; the LPLV will be December 1. Auditing of sites is ongoing.

The -019 (first-line therapy) enrollment has been completed on schedule; 787 subjects have been randomized and 175 have been directly enrolled into open-label therapy.

CMC Regulatory, Pharmaceutics R&D (Moreton) and MAP have developed plans for a pre-NDA-meeting with the FDA. We propose to do bioavailability studies with the 500/2.5 and the 500/5 tablets and comparative dissolution studies between the 250/1.25 and 500/2.5 tablets. A meeting with the FDA in early November is planned to discuss these and other issues.

Action: Meet with the FDA to discuss study plans leading to NDA filing.

ATTACHMENT R

Project Leader: M. Altmeyer

Project Manager: J. O'Sullivan

Metformin Hydrochloride Reformulation (BMS-207150)

PWG Meeting Summary

November 24, 1998

METFORMIN/GLYBURIDE

Issue: The CV138-011 study of second line therapy in patients with type 2 diabetes mellitus who are inadequately controlled on sulfonylurea monotherapy anticipates LPLV on Dec.1, 1998 and a report should issue mid-April, 1999. The CV138-019 first line therapy in patients who are drug naïve and inadequately controlled with diet and exercise expects LPLV May 20, 1999 and a report will issue Sept.7, 1999. Preliminary data from the open-label -019 study, in which patients were directly enrolled into open-label, show that patients treated with the metformin/glyburide combination for 13 weeks have a Hemoglobin A1c value of 6.8% compared with a baseline value of 10.3%; in the same study, fasting glucose levels drop from a baseline value of 267mg/dl to 162 mg/dl at two weeks, and 144mg/dl at week 13. These dramatic results are expected to have a significant impact on medical opinion.
Pilot bioavailability studies of Micronase to chose a lot that is comparable to the original reference lot have been concluded; there were no significant differences between the four lots tested with respect to Cmax or AUC.

Action: Convene a meeting to discuss the inclusion of the -019 study data in the Glucophage label (J. O'Sullivan).

ATTACHMENT #5

Metformin Clinical Working Group Minutes
December 21, 1998

Attendees: Mary Arnould, Ingrid Delaet, Jeanne Denes, Jim Gaiser, Harry Goyvaerts, David Henry, Don Hotchkin, Michael Keats, Howard Kessler, Helen Lee, Chen Lin, Renee Lippens, Jim McCarthy, Francine McCarty, John Merten, Joyce Milinowicz, Orna Niecestro, Joe O'Sullivan, Jo Ann Ottino, Beth Piper,

ATTACHMENT S-1

II. Fixed Metformin/Glyburide Combination Program

A. Report and Submission Timelines

Timelines for both studies have not changed; both studies are on target to meet report & submission timelines.

B. Study Updates

CV138-011 (second line therapy; U.S.): The last patient-last visit for the randomized study period occurred on December 3, 1998. A protocol amendment incorporating the administrative letter that allowed for an increase in dose of study drug will be issued before the end of 1998.

CV138-019 (first line therapy; U.S.): Study is progressing on target for last-patient last-visit of May 20, 1999. A protocol amendment incorporating the administrative letter that allowed for an increase in dose of study drug will be issued before the end of 1998.

C. Monitoring Issues

CRF lock for CV138-011 was Dec. 14; however, CRFs are still outstanding. M. Arnould to request feedback from Regional Monitors regarding prioritization of CV138-019 relative to other BMS studies.

D. Biostatistics and Data Management

CV138-011: Outstanding CRFs will be requested from sites and prioritized for review by BDM. Quest central lab is expected to provide a data tape December 24; this tape was delayed because of inconsistencies with the CRF regarding the fasting status of the patient. Long-term Statistical Analysis Plan in preparation.

CV138-019: For efficiency, CRFs for review by Clinical Scientists are provided in hard copy by BDM-Hopewell. Draft Statistical Analysis Plan for CV138-019 is circulating; a meeting of all reviewers is scheduled for early Jan. 1999. Long-term Statistical Analysis Plan is pending. Safety request will be submitted to Project Programming by early Jan. 1999. A list of protocol violations will be prepared by early Jan. 1999.

E. Regulatory Issues

Metformin Clinical Working Group Minutes
January 18, 1999

Attendees: Helen Badiak, Ingrid Delaet, Jim Gaiser, Cindy Graziano, David Henry, Donna Holland-O'Rourke, Don Hotchkin, Michael Keats, Howard Kessler, Helen Lee, Chen-Sheng Lin, Jim McCarthy, Kenny McCarthy, Francine McCarty, John Merten, Joyce Milinowicz, Joe O'Sullivan, Miranda Pans, Patti Peck, Beth Piper, Beth Proszynski, Warren Randolph, Joan Schmidt, Lynn Search, Marlene Skoloda,

ATTACHMENT S-2

II. Fixed Metformin/Glyburide Combination Program

A. Report and Submission Timelines

Both studies are on target to meet report & submission timelines. Revised timelines are in preparation; the open-label reports will be included. The submission date has tentatively been moved back to October 6, 1999.

B. Study Updates

CV138-011 (second line therapy; U.S.): Study has progressed to In-house Query Lock, Item 10 in timelines, which will be a few days late. A protocol amendment incorporating the administrative changes that allowed for an increase in maximal dose of study drug has been issued.

CV138-019 (first line therapy; U.S.): All patients should have Visit C113 by March 3. Since this visit represents a key efficacy point, data clean-up will be expedited with PID locks under consideration. A protocol amendment incorporating the administrative changes that allowed for an increase in maximal dose of study drug has been issued.

C. Monitoring Issues

Study teams will keep U.S. Regional Monitors informed about CRF & query locks, and any relevant changes in timelines. Regional Monitoring support for PID lock in March for Visit C113 in CV138-019 will be essential.

D. Biostatistics and Data Management

Data requests for the open-label reports will be forwarded to J. Gaiser.

CV138-011: A few CRFs are outstanding. Clean-up and preparation of tables for protocol violations and adverse events is in progress. Quest central lab has provided a data tape; inconsistencies with the CRF regarding the fasting status of the patient have been resolved. At least one more transfer of lab data from Quest will be needed. Draft Open-label Statistical Analysis Plan is circulating for review.

CV138-019: Statistical Analysis Plan will be finalized today (Jan 18). Long-term Statistical Analysis Plan is pending. Issues regarding discrepancies in labeling of visits by Quintiles central lab to be resolved.

Metformin Clinical Working Group Minutes
March 15, 1999

Attendees: Mary Arnould, Helen Badiak, Laura Cyriacus, Ingrid Delaet, Jeanne Denes, Jim Gaiser, Donna Holland-O'Rourke, Michael Keats, Carol Kiczek, Sue Kusek, Helen Lee, Kenny McCarthy, Francine McCarty, John Merten, Joyce Milinowicz, Orna Niecestro, Joe O'Sullivan, Miranda Pans, Patti Peck, Beth Piper,

ATTACHMENT S-3

II. Fixed Metformin/Glyburide Combination Program

A. Report and Submission Timelines

Both studies are on target to meet submission timelines. Revised timelines are in preparation; the long-term reports will be included. The NDA Task Force is meeting on a regular weekly/twice monthly basis.

B. Study Updates

CV138-011 (second line therapy; U.S.): First draft final study report for short term is in progress. The open-label final study report shell is circulating.

CV138-019 (first line therapy; U.S.): All patients have had Visit C113; on target for C197 LPLV visit by May 20. The report shell for the long-term phase is awaiting input from the Statistical Analysis Plan.

CV138-043: (second line therapy; U.S.): Protocol approved by PRC on March 5. Investigator Meeting is scheduled for March 20 in Arlington, VA. Three-hundred subjects projected to be randomized by July 7.

C. Clinical Drug Supplies

Open-label supplies for –019 may run short because direct enrollment into the long-term phase occurred after the initial projections. Options include use of extra supplies prepared for the –043 study and relabeling of randomized supplies from warehouse inventory.

Lead-in, double-blind, and partial long-term supplies for –043 are on target for availability on April 1.

D. Monitoring Issues

Regional Monitoring support for the following CRF locks is essential: –011, all long-term visits as of March 19 must be in-house by March 25, with source verification completed by April 1. Regional Monitors to instruct sites not to report duplicate adverse events.

E. Biostatistics and Data Management

CV138-011: The CRF tracking log for –011 has been modified to include long-term visits. Quest central lab will provide a memo clarifying the revision of lab reference ranges and the date of implementation.

CV138-019: Long-term Statistical Analysis Plan is pending completion of plan for -011.

Distribution
H. Pouleur
M. Staten
S. Anderson
M. Barnhart
P
P. Baumann
K. Carroll
J. Conroy
R. DeRegis
D. Hotchkin
M. Kantor
P. Lapuerta
D. MacNeil
T. Ott
M. Teter

Metformin Clinical Working Group Minutes
April 20, 1999

Attendees: Helen Badiak, Laura Cyriacus, Ingrid Delaet, Jim Gaiser, Dave Henry, Donna Holland-O'Rourke, Don Hotchkin, Michael Keats, Howard Kessler, Helen Lee, Chen-Sheng Lin, Kenny McCarthy, Francine McCarty, John Merten, Joyce Milinowicz, Orna Niecestro, JoAnn Ottino, Patti Peck, Beth Piper, Joan Schmidt, Sandra Smith, Peter

ATTACHMENT S-4

Fixed Metformin/Glyburide Combination Program

Report and Submission Timelines
Timelines have been revised to move up datalock for -019 to June 23. All items from Clinical have been moved up for delivery to WWRA by August 17. BMS is considering electronic submission of CRTs and CRFs for subjects who discontinued because of death or adverse events; a proposal must then be discussed with FDA. Amy Grant will develop timelines for preparation of the electronic components.

B. Study Updates
CV138-011 (second line therapy; U.S.): First draft FSR for short term was issued April 15; second draft expected by April 26.

CV138-019 (first line therapy; U.S.): On target for C197 LPLV visit by May 20.

CV138-043 (second line therapy; U.S.): Screening began on April 6. Seventy of 83 sites have drug.

C. Clinical Drug Supplies
Lead-in, double-blind, and partial long-term supplies for –043 were available on April 7.

D. Monitoring Issues
Monitoring Plan for –043 (S. Kusek, J. Milinowicz, O. Niecestro) is in progress.

E. Biostatistics and Data Management

CV138-011: Datalock for the long-term period is on track for April 30.

CV138-019: Draft long-term Statistical Analysis Plan is undergoing review. Subjects who enrolled directly into the long-term period will not be discussed in the short-term FSR, but will be included in the long-term FSR. Adverse events that occurred during the short-term phase will not be presented in the long-term FSR.

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Metformin Clinical Working Group Minutes
May 18, 1999

Attendees: Mary Arnould, Laura Cyriacus, Ingrid Delaet, Jeanne Denes, Jim Gaiser, Dave Henry, Donna Holland-O'Rourke, Don Hotchkin, Michael Keats, Howard Kessler, Helen Lee, Chen-Sheng Lin, Kenny McCarthy, Francine McCarty, John Merten, Joyce Milinowicz, Orna Niecestro, Joe O'Sullivan, Patti Peck, Beth Piper, Beth Proszynski, Warren Randolph, Lynn Search, Marlene Skoloda, Sandra Smith,

F. Regulatory Issues
Annual IND update was issued.

ATTACHMENTS-5

II. Fixed Combination Metformin/Glyburide Program

A. Report and Submission Timelines

Timelines have not changed; all clinical components are targeted for a mid-August delivery to Regulatory.

B. Study Updates

CV138-011 (second line therapy; U.S.): Executive sign-off meeting for double-blind FSR is scheduled for May 20; D. Henry will provide an efficacy table to complete report. The FSR shell for the open-label period has been submitted to CDMC; an internal draft of the FSR to be issued May 21.

CV138-019 (first line therapy; U.S.): On target for C197 LPLV visit by May 20.

All Case Report Forms for –019 double-blind period must be received by BMS by May 28; query lock is June 15. Queries are to be faxed back directly to the Clinical Scientist.

CV138-019: Statistical Analysis Plan for double-blind period will be amended to include post-prandial glucose excursions and early response with single once-daily dosing to assess potential contribution of components. The efficacy data request will be issued May 18. Draft open-label Statistical Analysis Plan to be finalized within 1 week, with efficacy data request to follow.

Subject: Minutes of metformin DCT
Date: Wed. 23 Jun 1999 17:07:30 -0400

ATTACHMENT S-6

Metformin/Glyburide Combination Tablet

A pre-NDA meeting with the FDA was held on May 24. At this meeting, the recent bioavailability results and particle size data obtained with the revised validated methodology was presented. The FDA agreed to the proposed three-point specification for bulk glyburide. FDA asked BMS to change the dissolution method for the metformin component to 50 rpm with paddles. Pharmaceutics R&D in Moreton have been able to generate dissolution data on approximately 24 batches with the 50 rpm speed. Based on these data, a QC method with 50 rpm will be implemented and a specification of 80% dissolved in 30 minutes will be proposed in the NDA.

Two lots from the Humacao site show slightly faster dissolution than the rest and do not quite meet the criteria for biowaiver based on in vitro dissolution. However, given that the absorption of metformin from marketed immediate release dosage forms is permeability limited and not absorption rate limited, and that the Semoy clinical lots are bioequivalent to Glucophage tablets, the differences seen can be argued as not significant. Analytical testing on 15 month samples from the Semoy stability study and 9 month samples from the Humacao stability study has been completed. Weekly CMC sub-team meetings are being held to follow-up on all activities for NDA submission.

The Lipha manufacturing facility in Semoy was recently audited by BMS quality assurance department and have issued a number of action items. The resolution of these items is needed prior to FDA inspection towards the end of October. BMS QA representatives along with J. Berg from BMS Tech Ops and M. Brown from WWRA-CMS will follow up on resolution of these action items.

Subject: Metformin DCT minutes
Date: Wed, 21 Jul 1999 13:21:53 -0400

ATTACHMENT S-7

Metformin/Glyburide Combination Tablet

The Lipha manufacturing facility in Semoy was recently audited by BMS quality assurance department and have issued a number of action items. BMS QA will go back to Lipha Semoy for another inspection in September and to ensure resolution of these items prior to FDA inspection towards the end of October. A. Dennis and M. Brown will discuss the validation protocol with Semoy.

Subject: fixed combo met/gly
Date: Tue, 03 Aug 1999 09:46:54 -0400
From: "Beth A Piper" <piperb@bms.com>
Organization: Bristol-Myers Squibb
To: Burton Rodney <burton.rodney@bms.com>

Bud -

The fixed combo started out as a line extension for glucophage. Traditionally with diabetes therapies, combination therapy has only been indicated for second line use, after a monotherapy has been found to be inadequate or no longer controlling a patiet's blood sugar.

Read & Understood RBR Pulse Aug 3, 1999

The concept of a fixed combination metformin/glyburide is not novel, it is marketed in 6-12 countries by various manufacturers. Both glyburide and metformin are older than I am but there is little to no data available on fixed combination use, I actually could only find two studies. the dosing is typically 400-500 mg of metformin with 2.5-5 mg of glyburide/glibenclimide or some other sulfonylurea.

When BMS approached the FDA about doing a fixed combination for second line therapy (with a 500/2.5 mg and 500/5 mg), the FDA replied that they wanted a firstline therapy trial as well. As it would be a single entity that might get used as first line or 'monotherapy' they wanted to know it would be safe in a different patient population or the population that did not yet require combination therapy for glycemic control. Approval depended upon safety trends as firstline therpy.

Not only was fixed combinaiton data hard to find but there was no data on combination therapy available as firstline treatment. From clinical experience I knew the planned dosing was too high for first line use and that we would see too much hypoglycemia compared to monotherapy. We then halved the 500/2.5 to get a 250/1.25 mg tablet strength. I knew it would work for glucose lowering and should be safe but didn't know how it would compare to monotherapy.

We couldn't have asked for better results. We beat placebo but were also statistically better than both glyburide monotherapy and metformin monotherapy with respect to glycemic efficacy. We have postive safety trends that the FDA was interested in, we are doing ad-hoc ananalysis in the ISS for both hypoglycemia and GI SE. We also got unexpected data that suggests that metformin has a postive or glucose sensitiziing effect on the pancreas. It is getting late I'll give you the deatils later.

Beth

SE = Side effects

ATTACHMENT T

Project Leader: R. Simon

Project Manager: J. O'Sullivan

Metformin (BMS-207150)
PWG Meeting Summary
August 31, 1999

METFORMIN GLYBURIDE COMBINATION TABLET

Issue: The CMC report, the MAP section and the –011 report are already complete and the –019 final study report, the label, the ISE and the ISS are near completion and should be in Regulatory early next week. We are still on track for a September 30 NDA filing.
Given the quality of the results described in the NDA filing and their medical importance, it is reasonable to believe that we stand a good chance of getting priority review by the FDA..

Action: Intensive effort will continue to ensure a September filing.

ATTACHMENT T-1

Project Leader: R. Simon

Project Manager: J. O'Sullivan

Metformin (BMS-207150)
PWG Meeting Summary
September 28, 1999

METFORMIN GLYBURIDE COMBINATION TABLET

Issue: The 52 volume submission and 2 CD-Rom discs are almost complete and will be shipped out on Sept. 30 for filing in Washington. The medical importance of the results described in the NDA filing should qualify this filing for Priority Review. We will know the decision of the FDA when their 45 day review is complete.

At least three Phase IIb studies are being planned: (1) a study similar to the –019 but with Actos replacing the placebo, (2) a direct comparison of Actos and the metformin/glyburide product and (3) a triple combination therapy with Avandia (agreement, in principle, has been reached with SKB on this). Other studies under consideration would be two pediatric studies (PK and efficacy) with the combo and, possibly, an insulin study. The pediatric study will begin 3 months after the approval of the combo (possibly May). Production scale-up in Humacao will begin this year or in January. Some lumping of the combo material has been seen and it may be necessary to screen the drug before tableting. A

PROPRIETARY INFORMATION - NOT FOR FURTHER DISTRIBUTION

ATTACHMENT 4

Manufacturing launch team needs to be assembled. [Post meeting note: the NDA was filed on Sept. 30]

Action: S. Canterberry will begin to assemble a launch team.

FIXED COMBINATION METFORMIN/GLYBURIDE PRODUCTS

APPLICATION SUMMARY

September 22, 1999

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Worldwide Clinical Research and Development
Bristol-Myers Squibb Pharmaceutical Research Institute
Bristol-Myers Squibb Company
Princeton, NJ 08534

ATTACHMENT U-1

1 INTRODUCTION

The diagnosis and management of Type 2 diabetes mellitus is rapidly undergoing progressive changes. It is now widely accepted that glycemic control significantly impacts on prognosis. The results of the DCCT (Diabetes Control and Complications Trial)[1] in patients with Type 1 diabetes and the UKPDS (United Kingdom Prospective Diabetes Study)[2,3,4,5] in patients with Type 2 diabetes, have confirmed that glycemic control to as near normal glucose levels as possible should be the therapeutic target to prevent the long-term microvascular and macrovascular complications of elevated blood glucose. The diagnosis of diabetes has undergone significant changes as evidenced by the new American Diabetes Association (ADA) diagnostic and classification guidelines.[6]

Oral therapeutic options for the treatment of Type 2 diabetes mellitus until recently, have been severely limited. Prior to 1995, sulfonylurea therapy had been the mainstay of oral diabetes agents in the United States. Sulfonylureas target the relative deficiency of endogenous insulin by augmenting insulin secretion from pancreatic islet cells. Since 1995, three new classes of agents have been added to the diabetes armamentarium for the management of hyperglycemia. Metformin, a biguanide, targets insulin resistance at the liver by decreasing hepatic glucose production and at the muscle by enhancing peripheral glucose uptake, and it has been suggested that metformin may play a role in preventing glucose desensitization of the islet cell.[7,8] Thiazolidinediones decrease peripheral insulin resistance and alpha-glucosidase inhibitors help control postprandial glucose excursion by delaying absorption of dietary carbohydrate. These agents are all indicated as monotherapy and some are indicated for use in combination therapy after monotherapy has been found to be inadequate.

The combination of metformin and a sulfonylurea have demonstrated a synergistic effect on glucose lowering when used in combination. Both drugs have been used in the treatment of diabetes for over 40 years. The different mechanisms of action in targeting hyperglycemia are complementary and make combination use an attractive and a rational course of action, even in drug naive patients. Thus, treatment with a fixed dose combination tablet may also be expected to improve glycemic control as either initial therapy in patients with Type 2 diabetes mellitus with inadequate control on diet and exercise, or as second line therapy in patients to achieve glycemic control at lower doses than either monotherapy with comparable or fewer potential side effects of the individual agents and with the same ease of administration.

Metformin used with a sulfonylurea is a known and effective combination in the treatment of Type 2 diabetes mellitus when either monotherapy has become inadequate. A fixed combination tablet of metformin and glyburide is not novel; though few publications exist, a number of fixed combination metformin/glyburide (400/2.5 mg) tablets are available outside the U.S. for this indication.[9,10] What is unique to this program is that in addition to evaluating fixed combination therapy as a second line treatment alternative, this clinical program evaluated the safety, efficacy and clinical utility of a low dose fixed combination metformin/glyburide as initial therapy in drug naive patients with Type 2 diabetes.

Two studies were conducted to demonstrate the complementary effects of metformin and glyburide in efficiently achieving improved glycemic control with a better or comparable safety and side effect profile in the treatment of Type 2 diabetes. Until now, no data had existed on the use of low dose combination therapy as first line therapy in patients inadequately controlled with diet and exercise. The BMS Protocol CV138-019 consists of a completed 32-week double-blind treatment phase with two dose strengths (250/1.25 mg, 500/2.5 mg) of fixed combination metformin/glyburide tablets, placebo,

glyburide and metformin as first line therapy in patients with Type 2 diabetes. Subjects participating in the double-blind treatment phase were also eligible to enter a 52-week ongoing open-label treatment phase to assess the long-term safety and durability of glycemic control with fixed combination metformin/glyburide titrated to a therapeutic target.

The BMS Protocol CV138-011 consists of a completed 16-week, double-blind treatment phase with two dose strengths (500/2.5 mg, 500/5 mg) of fixed combination metformin/glyburide tablets, metformin monotherapy or continued maximum dose glyburide monotherapy as second line treatment in patients who failed to achieve adequate glycemic control on at least one-half maximum dose glyburide monotherapy. Subjects participating in the double-blind treatment phase were also eligible to enter a 52-week ongoing open-label treatment phase to assess the long-term safety and durability of glycemic control with fixed combination metformin/glyburide titrated to a therapeutic target.

Formulation Development History

Introduction

Metformin hydrochloride is used in the treatment of Type II diabetes and belongs to a general class known as biguanides. Metformin is currently available as Glucophage® Tablets (brand of metformin hydrochloride), Bristol-Myers Squibb NDA 20-357. Glyburide is also used for the treatment of Type II diabetes and belongs to a class known as sulfonylureas. Glyburide single entity tablets are available as a number of different commercial products, however the designated reference product for generic equivalency is Micronase® (Pharmacia and Upjohn). The use of metformin hydrochloride in combination with glyburide in patients not controlled adequately by either monotherapy is well accepted, hence a convenient single tablet combination product was developed to aid patient compliance and appropriate glucose control. The combination product would also provide a convenient medication for the effective first line treatment of type II diabetes.

One of the key objectives of the pharmaceutical development program for metformin hydrochloride - glyburide combination tablets was to identify a suitable composition and process that would produce comparable glyburide and metformin hydrochloride bioavailability with respect to co-administered Micronase® Tablets (Pharmacia and Upjohn) and Glucophage® Tablets (Bristol-Myers Squibb). The safety and efficacy of the identified new product would be qualified by clinical studies. Considering the planned clinical development program for this new product it was agreed with the Agency that strict bioequivalence to Micronase® and Glucophage® was not required, although comparable bioavailability would be met. While achieving bioequivalence is desirable, it was recognized at the outset that there are technical formulation limitations, inherent to a metformin hydrochloride - glyburide combination product approach which may not allow an exact

match to the *in vivo* pharmacokinetic properties of single entity Micronase® and Glucophage® tablets when co-administered. For example, since metformin hydrochloride is a high dose drug and will represent the highest proportion of the finished product volume, the dosage unit physical properties are highly influenced by the metformin hydrochloride component. Attempts to minimize this influence are limited by the need to ensure an acceptable dosage unit size.

The metformin hydrochloride and magnesium stearate mixture (99.5 : 0.5% w/w) used in the manufacture of the combination drug product described in this submission is the same as that used in approved marketed, Glucophage® Tablets. Metformin hydrochloride is mixed with a small quantity of magnesium stearate to help reduce physical lumping (caking) that can occur during storage, particularly when transported in large drums, and to improve flow. The specifications for metformin hydrochloride/magnesium stearate (99.5 : 0.5% w/w) are the same as those already approved in Bristol-Myers Squibb NDA 20-357.

Metformin hydrochloride is freely soluble in water (approximately 300 mg/mL at room temperature) and shows good solubility across the physiological pH range (greater than 250 mg/mL), a pH solubility profile can not be drawn as metformin is a strong base and a saturated solution of metformin hydrochloride becomes self buffering[(1)]. Metformin hydrochloride has been reported to have two dissociation constants[(2)], measured as 2.8 and 11.5 at 32 °C.

Glyburide is a well characterized, compendial grade drug substance which has been used extensively in marketed products. It is virtually insoluble in water and is a weak acid with a reported[(3)] pKa of 5.3, hence glyburide only shows significant aqueous solubility under relatively alkaline pH conditions.

References

1. Analytical Profiles of Drug Substances, Volume 25, p. 243 – 293 (1998) edited by H. Brittain.
2. Clarke's Isolation and Identification of Drugs in Pharmaceutical body fluids and post mortem material, second edition, (1986) edited by A.C. Moffat., J.V.Jackson., M.S.Moss and B.Widdop.
3. Analytical Profiles of Drug Substances, Volume 10, p.337-403, (1981) edited by K.Florey.

Clinical Product Development

Formulation activities proceeded first with the metformin hydrochloride - glyburide 500 mg/2.5 mg tablet. After initial development was complete, formulations for additional product strengths (metformin hydrochloride - glyburide 500 mg/5 mg and 250 mg/1.25 mg tablets) were added. Development commenced based on the formulation and process that was already successfully employed for Glucophage® single entity tablets Table [II DP.T01]. The process for Glucophage® Tablets uses an aqueous povidone solution to granulate the metformin hydrochloride/magnesium stearate (99.5% : 0.5% w/w) in a high shear mixer. The granulation is dried in a fluid bed processor, size reduced and lubricated with magnesium stearate. In this process the final blend requires wetting to a specified moisture range prior to tablet compression. Bulk tablets are finally coated with a non-functional hydroxypropyl methylcellulose (HPMC) film coat. Incorporation of glyburide into this formulation, adding the glyburide at the dry blending step, resulted in tablets after compression that were soft and crumbled easily. The addition of extra-granular microcrystalline cellulose improved tablet compressibility, however, during exploratory stability testing under stress conditions of 40 °C/75%RH it was evident that this formulation approach was physically unstable and may not achieve consistent drug release properties, for example after 1 month the tablet disintegration time increased from approximately 12 minutes to greater than 20 minutes. This led to the introduction of the disintegrant croscarmellose sodium in the formulation to minimize possible changes in drug release during storage.

Table [II DP.T01] Formulation for Glucophage® (Metformin Hydrochloride) Tablets, 500 mg

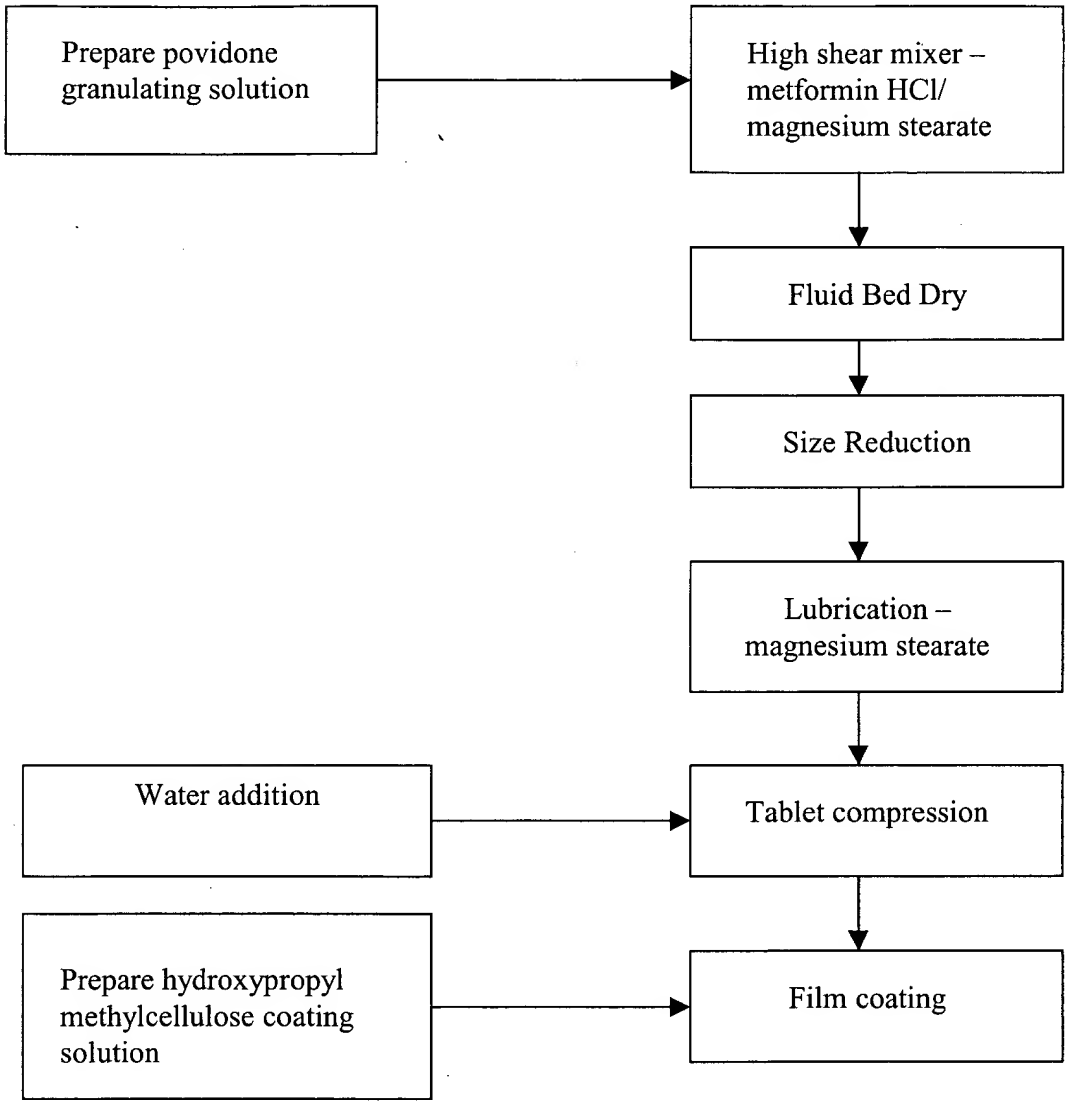
Ingredient	Quantity per Tablet (mg)
Metformin Hydrochloride/Magnesium Stearate (99.5 : 0.5% w/w)	502.5
Povidone USP	20
Purified Water[1], USP	q.s.
Magnesium Stearate, NF	2.5
TOTAL WEIGHT UNCOATED	**525.0**
Film coat composition	
Hydroxypropyl Methylcellulose, USP	4.0
Purified water[2], USP	q.s.
TOTAL WEIGHT COATED	**529.0**

q.s. quantity sufficient

1. Used to prepare povidone granulating solution, removed during drying. Water also added prior to compression.

2. Used to prepare coating solution, removed during drying

Schematic [II DP.S01] Glucophage® (Metformin Hydrochloride) Tablet Process Summary



During small scale development, the process was shown occasionally to produce product with a low glyburide content. This was attributed to preferential loss of glyburide during the dry mixing process to the exhaust filter sock of the high shear mixer. In an attempt to overcome this problem, the glyburide was added to the povidone granulating solution. The granulating solution containing the povidone and glyburide was added to the metformin hydrochloride/magnesium stearate and processed further as before.

Although this procedure produced acceptable glyburide product potency, a revised process avoiding the need to disperse the active drug substance in the povidone solution was investigated. By adding glyburide and croscarmellose sodium, incorporated together in the dry state, followed by addition to metformin hydrochloride/magnesium stearate in the high shear mixer, acceptable glyburide potency and unchanged dissolution properties during storage were still maintained. This resulted in the fundamental manufacturing process shown in schematic [II DP.S02] which was used during manufacture of the preferred investigational prototype (prototype 4, see below) through to the proposed commercial process.

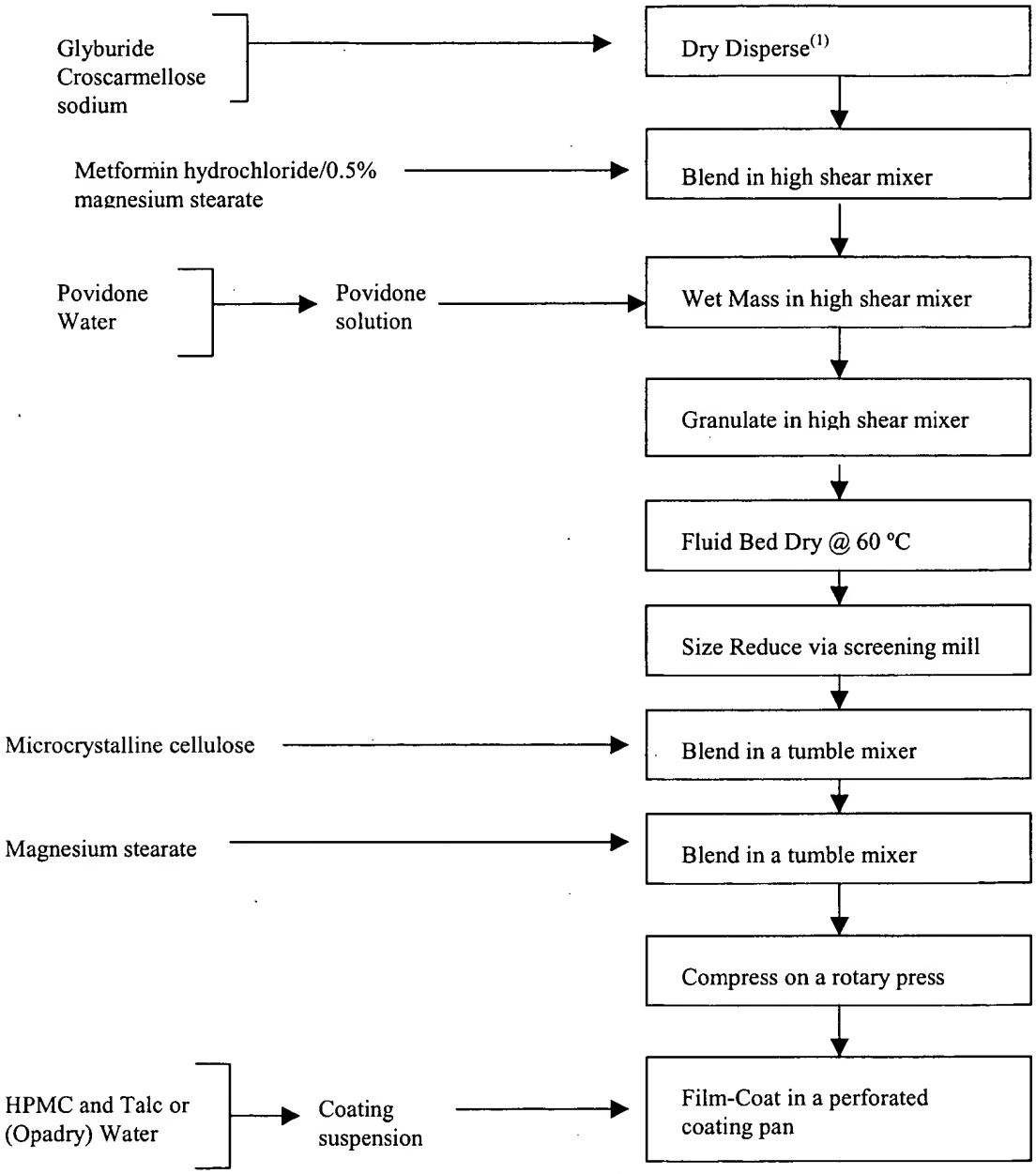
Since glyburide is a poorly soluble drug, particle size of the drug substance can be expected to have a significant effect on the rate of solution and hence also bioavailability. Therefore, in order to identify a product of suitable bioavailability for clinical studies to proceed, pre-clinical prototype products were manufactured using glyburide of different particle size distributions. A total of 5 prototype batches were prepared at small scale, of approximately 1 kg batch size, all using the same quantitative formulation (Table [II DP.TO2]). The only difference in manufacturing process amongst prototype batches 1 – 4 were the means by which glyburide was incorporated into the metformin hydrochloride/magnesium stearate (99.5 : 0.5% w/w) during the manufacturing process, i.e. either by first dispersing in the povidone binder solution (for prototype lots 1 and 2) or dry dispersed in croscarmellose sodium (for prototype lots 3 and 4). Prototype 5 was manufactured using a different process

and is hence not directly comparable to prototypes 1 - 4. Specifically, all the formulation ingredients were granulated together, unlike prototypes 1 - 4 where extra-granular microcrystalline cellulose is added to the dried granulation prior to tablet compression. For all these batches summary data concerning product manufacture and glyburide properties are summarized in Table [II DP.T02] and Table [II DP.T03].

The results of bioavailability studies conducted with prototypes 3 – 5 are presented in section 6 of this submission, the data relating to prototypes 1 and 2 is presented in the BMS report, Relative bioavailability of metformin – glyburide combination tablets compared to co-administered Glucophage® Tablets, BMS Accession No. 910062750, 1997, which can also be found in section 6. In summary, for formulation prototypes 1 – 4, which were processed in a similar way, the glyburide bioavailability was related to particle size. Batch number 970419A, referred to as prototype 4, demonstrated comparable bioavailability to Micronase® Tablets when co-administered with Glucophage® Tablets. For prototype 5 (different manufacturing process) glyburide bioavailability was lower than the desired range. As expected the metformin hydrochloride component was shown to be bioequivalent to Glucophage® when co-administered with Micronase® in all cases.

Based on data from these pilot bioavailability studies, the glyburide particle size distribution employed in prototype 4 was targeted for use in the clinical program.

Schematic [II DP.SO2] Overview of Manufacturing Process for Metformin Hydrochloride - Glyburide Tablets, 250 mg/1.25 mg, 500 mg/2.5 mg and 500 mg/5 mg



1. Dispersion of glyburide and croscarmellose sodium performed by bag mixing. This operation will be replaced by a tumble mixer for process validation.

Table [II DP.T02] Summary of Prototype Metformin Hydrochloride - Glyburide 500 mg/2.5 mg Tablets used for Pilot Bioavailability Assessment : Manufacturing

Ingredient	Product Batch Number/Description				
	961108	961110	970418A	970419A	M97023
	Prototype 1	Prototype 2	Prototype 3	Prototype 4	Prototype 5
	mg/tablet				
Metformin Hydrochloride/ Magnesium Stearate (99.5 : 0.5% w/w)	502.5	502.5	502.5	502.5	502.5
Glyburide	2.5	2.5	2.5	2.5	2.5
Croscarmellose Sodium	14.0	14.0	14.0	14.0	14.0
Povidone	20.0	20.0	20.0	20.0	20.0
Microcrystalline Cellulose	56.5	56.5	56.5	56.5	56.5
Magnesium Stearate	4.5	4.5	4.5	0.8	4.5
Talc	0.8	0.8	0.8	0.8	0.8
Hydroxypropyl Methylcellulose	12.0	12.0	12.0	12.0	12.0
Total	**612.8**	**612.8**	**612.8**	**612.8**	**612.8**
Batch Manufacturing					
Batch size (kg)	1.4 kg	1.4 kg	1.4 kg	1.4 kg	1.0 kg
Comment	Process fundamentally the same as used for subsequent clinical product, except glyburide added with povidone granulating solution		Process fundamentally the same as subsequently used for clinical supplies		Process significantly different to Prototypes 1 – 4, all materials granulated together.

Table [II DP.T03] Summary of Prototype Metformin Hydrochloride - Glyburide Tablets 500 mg/2.5 mg used for Pilot Bioavailability Assessment : Glyburide

	Product Batch Number/Description				
	961108	961110	970418A	970419A	M97023
	Prototype 1	Prototype 2	Prototype 3	Prototype 4	Prototype 5
Glyburide					
Source	Profarmaco	Secifarma	Guidotti	Profarmaco	Guidotti
Supplier Batch No.	240606	39/1	GLB 9614	241313	GLB 9503
Batch No.	SN/96/K7	SN/96/K6	SN/96/L2	SN/97/D10	13356
Glyburide Particle Size[1] (µm)					
D25%	15	28	10	6	13
D50%	33	58	25	11	30
D75%	62	88	52	19	58
Glyburide Dissolution[2] (mean % released)					
5 min.	18.0	18.3	26.9	31.6	8.7
10 min.	51.1	46.5	54.2	61.3	27.4
15 min	75.8	68.7	75.4	78.7	45.3
30 min.	100.1	92.9	97.2	99.9	83.1
45 min	103.2	96.3	100.5	100.0	93.5
Glyburide Bioavailability					
Protocol No.	CV138-009	CV138-009	CV138-017	CV138-017	CV138-017
C_{max} (ng/mL)	76.3	54.2	66.6	92.7	55.3
AUC (ng.h/mL)	493[3]	339[3]	531[4]	716[4]	440[4]

1. Particle size method CRM 8532-01 (SM248533)
2. pH 9.5 borate buffer, 75 rpm, USP Apparatus II (Reference LDH FP3 116)
3. AUC 0 – 24 hours
4. AUC 0 – 48 hours

At this stage, two additional strength products were developed from the prototype metformin hydrochloride - glyburide 500 mg/2.5 mg formulation for inclusion in the clinical program. The metformin hydrochloride - glyburide 500 mg/5 mg tablet strength employed the same composition except microcrystalline cellulose was replaced with the corresponding quantity of glyburide. The lower strength metformin hydrochloride - glyburide 250 mg/1.25 mg tablet was manufactured using the same granulation employed for metformin hydrochloride - glyburide tablets 500 mg/2.5 mg, but in this case the granulation was compressed at half the press weight. In all cases the clinical products were coated with the same non-functional HPMC based film coat. The two highest strength products were of similar appearance both being plain, white, *capsule* shaped tablets, whilst the metformin hydrochloride - glyburide 250 mg/1.25 mg product was a plain white, *round*, biconvex tablet. The quantitative composition and corresponding Product Identification Numbers for each clinical product strength is shown in tables [II DP.T04 – II DP.T06].

All clinical product supplies were manufactured in one of our intended commercial supply facilities (Lipha, Semoy, France). All glyburide drug substance lots used for manufacture were purchased from our intended commercial source (Profarmaco, Milan, Italy) and micronized to achieve a particle size distribution comparable to that used in the experimental lot, 970419A (Prototype 4). Lots SN/97/G1 and SN/97/J10 were prepared by micronization using small scale equipment, whilst all subsequent drug substance lots were size reduced by the drug substance vendor using commercial scale equipment of the same class (as defined in Guidance for Industry, SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms, Manufacturing Equipment Addendum) as that used on the smaller scale. In both cases, particle size reduction was performed using a fluid energy mill, specifically an Esco Strahlmuehle jet mill during early development and a Tarenzi jet mill during supply of later clinical and stability batches.

Long Term Stability Studies (LTSS)

Product has been manufactured for Long Term Stability Studies (LTSS) at two separate sites, both of which are intended commercial supply facilities. Manufacture of the first long term stability supplies occurred at the Semoy facility (Lipha, France) using the same core tablet formulation and manufacturing process already used for clinical supplies. The only difference between product manufactured for clinical and stability purposes was the film coat composition, and product shape for the metformin hydrochloride - glyburide 250 mg/1.25 mg tablet. Specifically, the clear film coat used on the clinical product was replaced with a colored system (Opadry II, Colorcon) to aid product differentiation and additionally for the lowest strength product (metformin hydrochloride - glyburide tablet, 250 mg/1.25 mg) the shape was changed from round to a capsule appearance, to match the shape of both higher product strengths. The tablets were also debossed with example markings, since at this stage final product markings were not confirmed.

Three batches of each product strength were manufactured (total of 9 batches). The metformin hydrochloride - glyburide 500 mg/5 mg tablets were manufactured at a batch size of 240 kg (400,000 tablets). The metformin hydrochloride - glyburide 500 mg/2.5 mg and metformin hydrochloride - glyburide 250 mg/1.25 mg tablets are compressed from a common granulation, hence the batch sizes employed in these cases were 405 kg for the common granulation, which when divided equally into two 202.5 kg batches for compression of each strength product, produced a theoretical batch size of 337,500 tablets and 675,000 tablets respectively. Tablets were packaged in 100, 500 and 5000 count HDPE bottles and PVC/aluminum foil blisters. Long term stability studies commenced at Moreton (BMS, UK) in December 1997 and a total of 15 months data is presented in the submission. Stability studies are detailed in Section II.G.1.

Long term stability supplies were subsequently also manufactured at the BMS facility in Humacao, Puerto Rico. At this time minor changes in product appearance were introduced to reflect the final commercial image, specifically stability supplies now included the final tablet markings and a small bevel on all tablet strengths. Metformin hydrochloride - glyburide 500 mg/5 mg tablets were manufactured at a batch size of 200 kg (333,333 tablets). For metformin hydrochloride - glyburide 500 mg/2.5 mg tablets and metformin hydrochloride - glyburide 250 mg/1.25 mg tablets the common stock granulation was manufactured at a 200 kg scale, which when divided equally into two 100 kg batches for each strength product, produced a theoretical batch size of 166,666 tablets and 333,333 tablets respectively. Tablets were packaged in 100, 500 and 5000 count HDPE bottles using the intended commercial bottle sizes. Long term stability studies commenced at Covance, Harrogate, UK (co-ordinated by BMS, UK) in July 1998, a total of 6 months stability data is presented in the submission, which is in addition to that provided for product manufactured at the Lipha facility in Semoy, France. A general stability data discussion can be found in section II.G.3.

Clinical and Commercial Tablet Product Comparison

In summary, the tablet core composition is identical for clinical and all stability supplies. For the intended commercial product the non-functional clear film coat is replaced with a similar non-functional colored (Opadry II, Colorcon) film coat. In terms of markings, the clinical products are all plain, whereas the commercial product will be debossed. The overall tablet shape is the same for both 500 mg/2.5 mg and 500 mg/5 mg tablets, whereas the clinical 250 mg/1.25 mg tablet is round and the final commercial product is a capsule shape. These properties are summarized in Tables [II DP.T04] – [II DP.T06].

Table [II DP.T04] Comparison of Clinical and Long Term Stability (Semoy and Humacao) Metformin Hydrochloride - Glyburide 250 mg/1.25 mg Tablet Composition (mg/tablet)

Ingredient	Clinical	Stability
	Product Identification No. 207150-K999-017	**Product Identification Nos. 207150-K999-022[1] 207150-K999-041**
Metformin Hydrochloride/ Magnesium Stearate[2] (99.5 : 0.5% w/w)	251.25	251.25
Glyburide [3]	1.25	1.25
Croscarmellose Sodium	7.00	7.00
Povidone	10.00	10.00
Purified Water [4]	q.s.	q.s.
Microcrystalline Cellulose	28.25	28.25
Magnesium Stearate	2.25	2.25
TOTAL WEIGHT UNCOATED[5]	**300.00**	**300.00**
Film Coat Composition		
Hydroxypropyl Methylcellulose (Methocel E15)	6.0	-
Talc	0.5	-
Opadry OY-L-22903[6]	-	6.0
Purified Water[7]	q.s.	q.s.
TOTAL WEIGHT COATED	**306.5**	**306.0**

1. Product Identification Numbers are different to record change in tablet appearance (example debossing and final debossing) and introduction of a small bevel edge to the tablet. Product Identification Number 207150-K999-041 is assigned to the commercial product.
2. Contains 99.5% w/w metformin hydrochloride and 0.5% w/w magnesium stearate. Assumes 100.0% purity of metformin hydrochloride component.
3. Amount assumes 100.0% purity of glyburide.
4. For processing purposes only removed during drying of granule and tablet cores prior to film coating.
5. Target weight is adjusted based on in-process moisture determination.
6. Opadry OY-L-22903 contains HPMC, 2910 USP and talc as present in the clinical product, and in addition iron oxide yellow, lactose monohydrate, titanium dioxide and polyethylene glycol 4000.
7. Water used for processing only. Removed during film-coating.

Table [II DP.T05] Comparison of Clinical and Long Term Stability (Semoy and Humacao) Metformin Hydrochloride - Glyburide 500 mg/2.5 mg Tablet Composition (mg/tablet)

Ingredient	Clinical	Stability
	Product Identification No. 207150-K999-008	**Product Identification Nos. 207150-K999-021[1] 207150-K999-042**
Metformin Hydrochloride/ Magnesium Stearate[2] (99.5 : 0.5% w/w)	502.5	502.5
Glyburide [3]	2.5	2.5
Croscarmellose Sodium	14.0	14.0
Povidone	20.0	20.0
Purified Water [4]	q.s.	q.s.
Microcrystalline Cellulose	56.5	56.5
Magnesium Stearate	4.5	4.5
TOTAL WEIGHT UNCOATED[5]	**600.0**	**600.0**
Film Coat Composition		
Hydroxypropyl Methylcellulose (Methocel E15)	12.0	-
Talc	1.0	-
Opadry OY-L-24808[6]	-	12.0
Purified Water[7]	q.s.	q.s.
TOTAL WEIGHT COATED	**613.0**	**612.0**

1. Product Identification Numbers are different to record change in tablet appearance (example debossing and final debossing) and introduction of a small bevel edge to the tablet. Product Identification Number 207150-K999-042 is assigned to the commercial product.
2. Contains 99.5% w/w metformin hydrochloride and 0.5% w/w magnesium stearate. Assumes 100.0% purity of metformin hydrochloride component.
3. Amount assumes 100.0% purity of glyburide.
4. For processing purposes only removed during drying of granule and tablet cores prior to film coating.
5. Target weight is adjusted based on in-process moisture determination.
6. Opadry OY-L-24808 contains HPMC, 2910 USP as present in the clinical product, and in addition iron oxide yellow, red and black, lactose monohydrate, titanium dioxide and polyethylene glycol 4000.
7. Water used for processing only. Removed during film-coating.

Table [II DP.T06] Comparison of Clinical and Long Term Stability (Semoy and Humacao) Metformin Hydrochloride - Glyburide 500 mg/5 mg Tablet Composition (mg/tablet)

Ingredient	Clinical	Stability
	Product Identification No. 207150-K999-009	**Product Identification Nos. 207150-K999-020[1] 207150-K999-043**
Metformin Hydrochloride/0.5% Magnesium Stearate[2] (99.5 : 0.5% w/w)	502.5	502.5
Glyburide [3]	5.0	5.0
Croscarmellose Sodium	14.0	14.0
Povidone	20.0	20.0
Purified Water [4]	q.s.	q.s.
Microcrystalline Cellulose	54.0	54.0
Magnesium Stearate	4.5	4.5
TOTAL WEIGHT UNCOATED[5]	**600.0**	**600.0**
Film Coat Composition		
Hydroxypropyl Methylcellulose (Methocel E15)	12.0	-
Talc	1.0	-
Opadry OY-L-32920[6]	-	12.0
Purified Water[7]	q.s.	q.s.
TOTAL WEIGHT COATED	**613.0**	**612.0**

1. Product Identification Numbers are different to record change in tablet appearance (example debossing and final debossing) and introduction of a small bevel edge to the tablet. Product Identification Number 207150-K999-043 is assigned to the commercial product
2. Contains 99.5% w/w metformin hydrochloride and 0.5% w/w magnesium stearate. Assumes 100.0% purity of metformin hydrochloride component.
3. Amount assumes 100.0% purity of glyburide.
4. For processing purposes only removed during drying of granule and tablet cores prior to film coating.
5. Target weight is adjusted based on in-process moisture determination.
6. Opadry OY-L-32920 contains HPMC, 2910 USP as present in the clinical product, and in addition iron oxide yellow, red, D & C yellow No. 10 aluminum lake, lactose monohydrate, titanium dioxide and polyethylene glycol 4000.
7. Water used for processing only. Removed during film-coating.

The overall manufacturing process used at Humacao, representing the final commercial image, remained the same as employed for clinical and stability product made at Semoy, see Schematic [II DP.S02], a detailed comparison is provided in Section II.E.1. To accommodate small differences between sites, for example with the granulation size reduction step where equipment is of the same class but different sub-class (as per Guidance for Industry SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms, Manufacturing Equipment Addendum) for Scale-up and Post Approval Changes: Immediate Release Products SUPAC-IR) processing conditions were selected to produce similar granulation particle size distributions to that achieved in Semoy.

In addition, a range of *in vitro* drug release comparisons have been conducted to qualify the similarity of the clinical and commercial products relative to reference lots manufactured at Semoy, France. The metformin hydrochloride - glyburide 500 mg/2.5 mg and 500 mg/5 mg reference batches were the subject of a definitive bioavailability study comparing the combination product bioavailability to co-administered Micronase® Tablets and Glucophage® Tablets (detailed in section 6). The metformin hydrochloride - glyburide 250 mg/1.25 mg reference batch was compressed from the same granulation as the 500 mg/2.5 mg reference batch. The comparative dissolution testing approach was submitted to the metformin/glyburide IND #, 52,837 in Submission No. 030 and presented to the FDA during a pre-NDA meeting on December 4, 1998.

The product comparisons can be split into three categories.

- *In vitro* dissolution tests to assure equivalence between the commercial formulation (test) and the clinical formulation (reference), both manufactured at Semoy.

- *In vitro* dissolution tests to assure equivalence between the commercial formulation

manufactured at Humacao, Puerto Rico (Test) and Semoy, France (Reference).

- *In vitro* dissolution tests to assure equivalence between the two metformin hydrochloride - glyburide products (500 mg/2.5 mg and 250 mg/1.25 mg) manufactured from the same stock granulation, as part of a bio-waiver for the 250 mg/1.25 mg product strength.

The dissolution testing conducted was based on the Guidance for Immediate Release Solid Oral Dosage Forms : Scale-up and Post approval changes: Chemistry, Manufacturing and Controls, *In vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation and the Guidance for Industry : Dissolution Testing of Immediate Release Dosage Forms.

To qualify the equivalence of the drug release properties between the clinical tablet formulation and commercial formulation (Semoy) and between the commercial formulation manufactured at Humacao and Semoy, full dissolution profile testing was conducted using the proposed QC methods for both metformin hydrochloride and glyburide. All dissolution profile data was analyzed according to standard Similarity Factor and Difference Factor calculations.

In order to verify equivalent performance and support a request for a waiver of bioequivalence testing for the 250 mg/1.25 mg tablet, manufactured from the same stock granulation as the 500 mg/2.5 mg strength, drug release profile comparisons were conducted in a total of three different pH media for both metformin hydrochloride and glyburide components.

The conditions employed for metformin hydrochloride drug release evaluation included in all cases a pH 6.8 phosphate buffer using USP Apparatus II (paddles) at a rotor speed of 50 rpm (proposed QC method) and, where appropriate, for additional testing, a pH 4.5

acetate buffer and 0.1N HCl acid, also using USP apparatus II at 50 rpm. For glyburide drug release evaluation, the conditions tested included, in all cases, a pH 9.5 borate buffer with USP Apparatus II (paddles) at a rotor speed of 75 rpm (proposed QC method, as per the Guidance for Glyburide for *In Vivo* Bioequivalence and *In Vitro* Dissolution Testing). In addition two other media test conditions were used for glyburide. Due to poor aqueous solubility and its weakly acidic nature, possessing a pKa of approximately 5.3, it is not possible to select a wide range of pH media representing physiological conditions since adequate sink solubility can not be achieved, even when using solubilizing agents. However, two media were identified that provided as broad a range of pH conditions that solubility constraints would allow, specifically a pH 6.4 phosphate buffer with 1% sodium lauryl sulphate and a pH 8.0 borate buffer. Both buffer systems used USP Apparatus II (paddles) at a rotor speed of 50 rpm.

The dissolution equivalence testing program is reviewed in detail in Section II.F.7 and II.F.8.

Bioavailability Studies and Glyburide Particle Size

A definitive bioavailability study has been conducted (CV138-024) to determine the relative bioavailability of the metformin hydrochloride and glyburide components of the combination product compared to the co-administered single entity products Glucophage® and Micronase® respectively, using metformin hydrochloride - glyburide tablets (500 mg/5 mg and 500 mg/2.5 mg) from the Semoy facility. The study results indicated that the metformin hydrochloride component was bioequivalent with respect to Glucophage® and that the glyburide component was of comparable bioavailability to Micronase®, meeting the study objectives. This study is reviewed in detail in Section 6.

An additional bioavailability study (CV138-042) was conducted to characterize the bioavailability of different glyburide drug substance lots used in the combination product, to assist establishment of final drug substance particle size specifications. Three batches of metformin hydrochloride - glyburide 500 mg/2.5 mg tablets were compared, each using a different glyburide drug substance lot, as described below.

Product Batch 9101 (glyburide lot SN/97/G1)
Product Batch 9118 (glyburide lot 268484)
Product Batch 9117 (glyburide lot 268585)

Drug product batch number 9117 was considered the reference lot since this batch was used in the definitive bioavailability study (CV138-024). Drug product batch 9118 (stability product) contained glyburide of typical particle size (lot 268484), whilst batch 9101 (clinical product) contained glyburide drug substance (lot SN/97/G1) which represented the largest particle size used in clinical studies. When compared to the reference lot, the test batch 9118 was shown to be bioequivalent, however lot 9101 did not demonstrate bioequivalence.

Based on this study, the proposed particle size specification for glyburide will exclude a particle size distribution similar to that of lot SN/97/G1.

During product development, the laser light scattering particle size methodology underwent improvement to ensure agglomerates of cohesive drug substance were reproducibly dispersed. Using the final validated method, all drug substance lots were re-measured. The rationale for establishing a particle size specification for glyburide was based on the particle size of glyburide used in the definitive bioavailability study (Study CV138-024), further *in vivo* evaluation of drug product made with glyburide lots of differing particle size (Study CV138-042), the experience of various clinical lots and the particle size method precision. The approach used was presented at a pre-NDA CMC meeting with the Agency and submitted to the metformin hydrochloride - glyburide IND # 47,342 (Submission No. 193). This approach was considered acceptable to the FDA. The specification derived is detailed in section I.D.1 and summarized below .

The mass median particle size (50% undersize value) must be between 7-10 um, the particle size representing the lower quartile (25% undersize) should not be greater than 6 um and the particle size representing the upper quartile (75% undersize) should not be greater than 23 um.

Conclusion

Bioavailability studies conducted on typical combination product lots representing the commercial process have demonstrated the metformin hydrochloride component to be bioequivalent relative to Glucophage® and the glyburide component to be of comparable bioavailability relative to Micronase® when the single entity products are co-administered. Using glyburide drug substance complying with our proposed particle size specification,

glyburide bioequivalence to a reference lot (batch 9117) has been demonstrated, confirming the reproducibility of drug exposure, in terms of average AUC and C_{max} values.

Stability studies conducted on product manufactured at both proposed commercial facilities (Semoy, France and Humacao, Puerto Rico) demonstrate acceptable stability properties and will enable a suitable expiration date to be agreed for room temperature storage conditions.